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NON-SUPPURATIVE HEPATITIS: A STUDY OF ACUTE AND CHRONIC FORMS WITH SPECIAL REFERENCE TO BIOCHEMICAL AND HISTOLOGICAL CHANGES.

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IT is the purpose of this paper to record some observations which have been made on thirty-two patients suffering from non-suppurative hepatitis, most probably caused by a virus infection. The disease was encountered in both its acute and its chronic forms. The study has been made by means of clinical observation, biochemical tests for liver function and material obtained either by the aspiration biopsy technique or at operation.

The virus disease which is now called "infectious hepatitis" has come into prominence as a result of its prevalence during the two world wars. The term "catarrhal jaundice" has until recent times been applied to this condition. The description by Virchow[(1)] in 1864 of a catarrhal inflammation in the duodenum and larger biliary passages as the cause of the jaundice was responsible for this conception. In 1920 Eppinger,[(2)] examining material from cases in the first world war, found evidence of degeneration in the liver cells, but no sign of catarrhal obstruction. Finally biopsy studies during the acute phase of the disease by Iversen and Roholm[(3)] in 1939 and by Dible *et alii*[(4)] in 1943 have produced direct evidence against the catarrhal conception of the disease.

The acute form of infectious hepatitis is well known in Australia, and often minor outbreaks occur, especially amongst children and young adults in schools and institutions. The description by Pickles[(5)] in 1928 of an outbreak of infectious hepatitis in a school in Wensleydale, Yorkshire, has become an epic in medical history. Later descriptions in both England and America by Cameron,[(6)] by Sodeman,[(7)] by Paul[(8)] and by Hardy[(9)] tell of the recent advances in our knowledge of this disease. They also make reference to homologous serum jaundice, a disease caused by a similar virus but showing several important differences. As a rule infectious hepatitis is not a fatal disease, but during the second world war it took its toll. In America Lucke,[(10)] working in the Army Medical Museum in Washington, D.C., has placed on record a comprehensive account of the autopsy findings in the service cases. Watson and Hoffbauer[(11)] stress the importance of recognizing the severe form of the disease with profound toxæmia, deep jaundice, clay-coloured stools and often pruritus. It may thus simulate extrahepatic obstruction from stone or carcinoma. Our series includes one fatal case which belongs to this group (Case 9).

The chronic form of hepatitis encountered in the present series usually began with an acute attack which resembled acute infectious hepatitis, but the disease process was prolonged, being finally characterized by chronic ill health with relapsing jaundice, weakness, loss of appetite and general despondency. Some chronic cases began insidiously with malaise, faint jaundice and an aching pain in the region of the liver.

The disease may be recognized for the first time in its chronic form, because the acute attack was not accompanied by jaundice and so escaped diagnosis. Thus Paul[(8)] showed that during an epidemic of hepatitis in America there was a parallel rise in cases of unexplained fever. Alternatively, the initial illness may have been so mild as to be ignored by the patient. Pollock[(12)] investigated an epidemic of hepatitis amongst the staff and children of a residential nursery school. One child developed a typical attack of acute infectious hepatitis with jaundice. The study of the other children then began, and during the ensuing ten weeks four of seventeen children had a

[1] Aided by a grant from the National Health and Medical Research Council.
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rise in the bilirubin content of the urine on more than one occasion. In a control series, studied in another institution where there was no known contact, there were no positive results to tests for bilirubin.

Neefe[13] carried out experimental studies, using human volunteers in whom the disease was induced by the ingestion of fæces from a case of acute infectious hepatitis. The histories of three of his volunteers (approximately a tenth of the total infected) were of great interest. They developed acute symptoms of hepatitis twenty-four, thirty-two and twenty-one days respectively after infection, two showing overt jaundice and the third showing no skin pigmentation but a rise in the serum bilirubin content to 1·9 milligrammes per 100 millilitres. They then passed into a chronic phase of hepatitis without jaundice lasting for periods between six and twelve months. The diagnosis of chronic hepatitis was based on the symptoms (periodic lassitude, weakness, nausea and pain over the liver), on laboratory evidence of hepatic disturbance, and, in two cases, on liver biopsy. The biopsy findings were confirmed by Lucke.

The chronic cases in the present series will be described in some detail as they form a most important group with regard to their recognition, management and prognosis. Some of them began with an acute attack of hepatitis, and later, when the patients were seen in the chronic stage, the clinical features and biochemical findings closely resembled the changes seen in the acute disease. Moreover, the histological changes in the liver were suggestive of a progressive lesion. Experience with service cases also leads us to believe that in the chronic group we are dealing with a chronic form of virus hepatitis. Similar cases to ours have been described by Lucke,[10] by Paul[8] and by Banck and Cheskin.[14] These cases have been ascribed to a virus infection.

Recently Watson and Hoffbauer[11] in America have made a comprehensive study of the chronic form of the disease, and they also believe that it is a continuation of the acute form of infectious hepatitis. They describe the "continuous chronic form" of the disease with chronic ill health and relapses. One of their female patients had suffered from hepatitis for thirty-four years. Her illness began with a classical acute attack, and her sister had a similar attack at the same time, but recovered in a few weeks.

In Denmark, Alsted[15] has reported a considerable rise in recent years in the number of fatal cases of hepatitis. This increase was almost entirely due to deaths amongst females over the age of forty-five years. He observed this sex and age incidence not only in his own series of 82 cases, which occurred in Copenhagen and in many respects resembled infectious hepatitis, but also in fatal cases of hepatitis occurring throughout the whole of Denmark. This latter group included all forms of hepatitis and cirrhosis. Alsted is unable to explain this high incidence in elderly women, nor is he confident that they were suffering from the virus disease "infectious hepatitis", which usually attacks children and young adults with an equal incidence in both sexes.

In Victoria, where most of the cases in the present series began, infectious hepatitis is endemic in the civilian population, and there has been no major outbreak during the past ten years. However, a number of servicemen have returned to the State from overseas during the past seven years, and it is possible that some of these may be suffering from a chronic form of the disease. Some recognized chronic sufferers were invalided back to the military hospitals with "chronic infectious hepatitis". Case 23 has been included in this series as the patient is representative of such a group. In the year 1942 a number of American troops, suffering from homologous serum jaundice following yellow fever vaccination, were admitted to an American military hospital in Melbourne. These cases have been described by Hayman.[16]

The Infective Agent.

In the present study no attempt was made to isolate the virus of infectious hepatitis by inoculation of human volunteers, which is the only known method of making a detailed study of the organism under controlled conditions. No laboratory animal is susceptible to the virus, and attempts to discover a satisfactory serological test have so far proved to be of little value (Miles[17]).

Extensive investigations, in both England and America, have recently thrown much light upon the ætiology of infectious hepatitis and the allied disease homologous serum jaundice. During the second world war infectious hepatitis was frequently encountered amongst service personnel, and several valuable contributions to our knowledge of the disease have been made, notably by Cameron,[6] by Gelliss *et alii*,[18] by Stokes *et alii*,[19] by Paul *et alii*,[20] by Bradley[21] and by Havens *et alii*.[22] The virus has been transmitted to human volunteers by using infected serum, fæces, urine or throat washings. The incubation period was found by Havens[23] to be between twenty and forty days, the average being twenty-four. The infective material was obtained from a patient in the acute phase of infectious hepatitis. Stokes[24] and his co-workers found that chlorination of infected water by the standard methods sometimes failed to kill the virus. It was also claimed by Havens[25] that one attack of the disease produced an immunity to further experimental infections by the virus of infectious hepatitis. And lastly, Gellis *et alii*[18] and Stokes *et alii*[19] provided evidence that pooled γ globulin provided some passive immunity to infectious hepatitis when injected intramuscularly.

Homologous Serum Jaundice.

Recent studies by Neefe,[26] by Hayman,[16] by Freeman,[27] by Bradley[21] and by Spurling *et alii*[28] and others have established the identity of a second virus which closely resembles the virus of infectious hepatitis, but shows differences with regard to immunity reactions, incubation period and method of transmission. Before the outbreak of the first world war the danger of transmitting infectious jaundice by the injection of infected human serum was recognized. Findlay *et alii*[29] have reviewed the history of our knowledge of this danger. This disease caused grave concern in the second world war, when it was found that a widespread outbreak of jaundice followed the administration of yellow fever vaccine to American troops. In the course of preparation of this vaccine human serum was added to suspend the virus, and this serum was found to be contaminated with a virus which caused acute hepatitis (Havens[25]). Findlay[29] concludes that homologous serum jaundice has an incubation period varying from forty-five to one hundred days, usually sixty to ninety days. Therefore the disease may have been transmitted as long as five months before jaundice first developed.

The virus is transmitted by injection of infected human blood, plasma or serum. The quantity of serum necessary to transmit the virus may be very small, so that failure to sterilize an infected needle may lead to its transmission. The virus survives heating to 56° C. for one hour, storage with freeze-dried yellow fever vaccine for one and a half years, or exposure to a 0·25% solution of phenol (Bradley[21]). Hughes[30] has shown that during an intramuscular injection there is some regurgitation of blood up the needle into the syringe after the pressure on the plunger is released. The infection may thus be spread by the syringe when several patients are injected with penicillin from the same syringe, even though the needle is changed after each injection. The virus has not been transmitted by fæces, urine or throat washings from a patient with an active infection, thus differing from that of infectious hepatitis; nor does there appear to be any cross-immunity between the two diseases (Havens[25]). On the other hand, both viruses seem to produce similar symptoms and clinical signs. Also the results of liver function tests and the histological changes in the liver are similar (Lucke and Mallory[31]).

Thus when a group of cases is studied, it is frequently impossible to determine the nature of the virus in any one instance. The history may provide a clue, but human experiment alone can provide the answer. Moreover, it may be that a different and as yet unidentified virus produces the chronic form of the disease. The virus of homologous serum jaundice may have caused the hepatitis

ILLUSTRATIONS TO THE ARTICLE BY DR. I. J. WOOD AND OTHERS.

FIGURE IV. Case 9; acute hepatitis, massive liver cell necrosis. Death seven weeks after onset. Autopsy specimen showing wrinkling of the capsule and scattered areas of hyperplastic liver tissue in a homogeneous background.

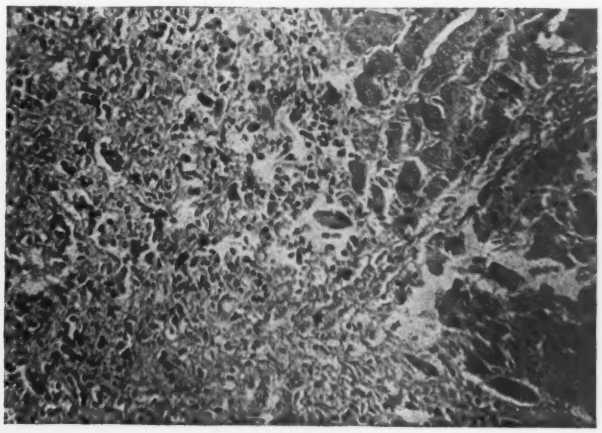


FIGURE V. Case 9: acute hepatitis; microscopic section showing a nodule of regenerating liver cells surrounded by acellular stroma containing collapsed sinusoids, bile ducts and inflammatory cells. (Hæmatoxylin and eosin stain, ×164.)

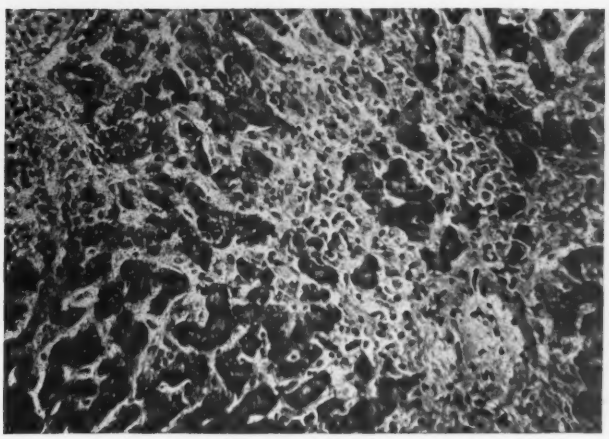


FIGURE VI. Case 17: acute hepatitis; aspiration biopsy specimen (twelve days after onset), showing central vein region occupied by granulation tissue and regenerating liver cells. (Best's carmine stain, ×164.)

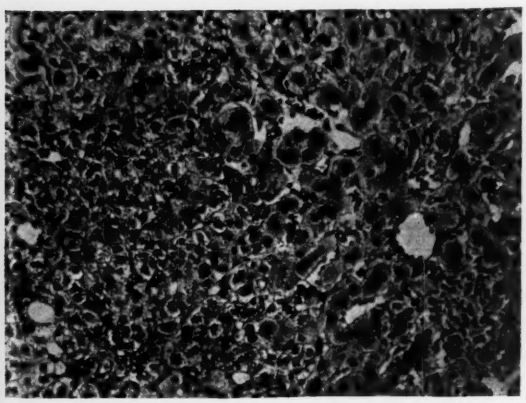


FIGURE VII. Case 14: acute hepatitis; aspiration biopsy (six weeks after onset), showing almost complete restoration of normal architecture. Note hyperplastic liver cells in the region of the central vein and the residual cellularity throughout the whole lobule. (Hæmatoxylin and eosin stain, ×164.)

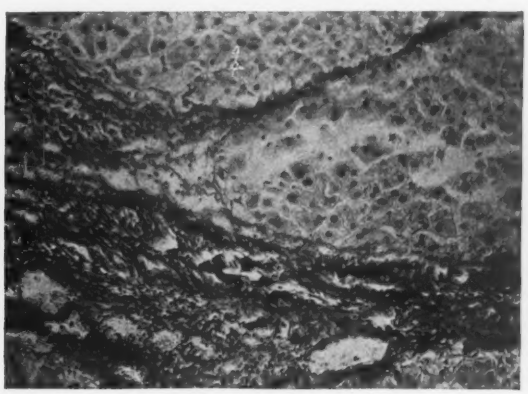


FIGURE X. Case 28: chronic hepatitis; high-power view of section stained by Van Gieson's method to show the fibrous tissue band intersecting islands of hyperplastic liver cells. The connective tissue shows very little infiltration with inflammatory cells (×120).

ILLUSTRATIONS TO THE ARTICLE BY DR. I. J. WOOD AND OTHERS.

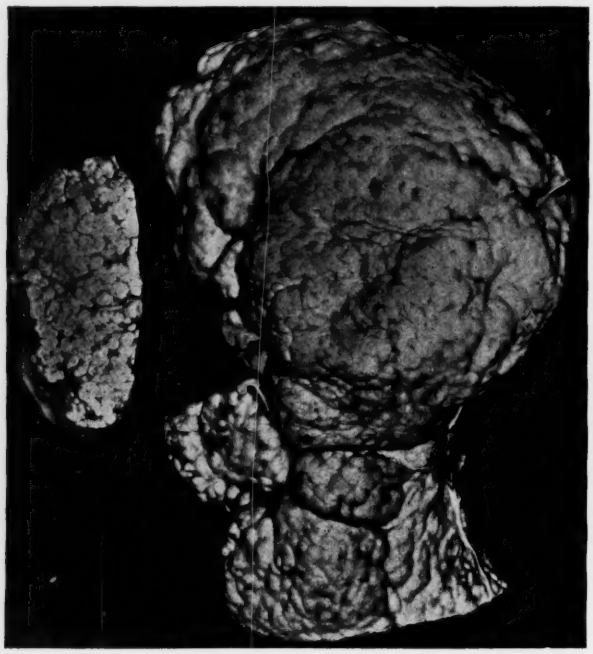


FIGURE VIII. Case 28: chronic hepatitis, multiple nodular hyperplasia. Death from liver failure eight months after original attack of hepatitis.

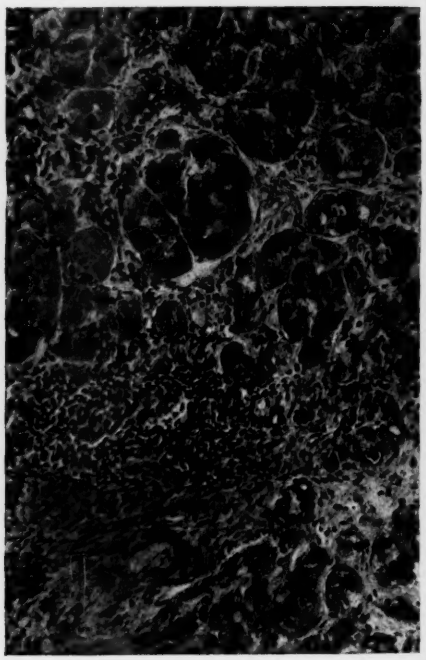


FIGURE XI. Case 21: chronic hepatitis; aspiration biopsy (nine weeks after onset) showing islands of regenerating liver tissue surrounded by cellular connective tissue. (Best's carmine stain, x 164.)

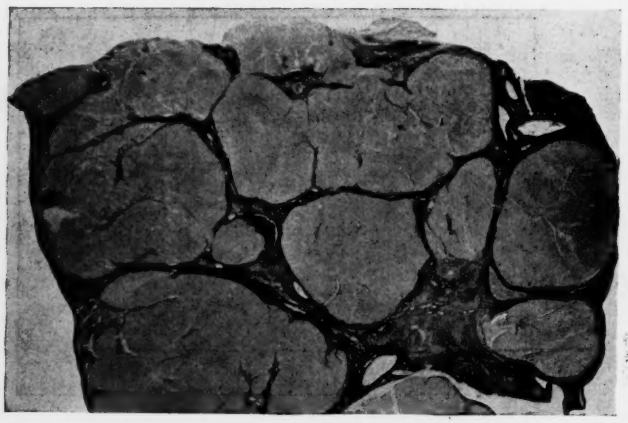


FIGURE IX. Case 28: chronic hepatitis; low-power view of section stained by Van Gieson's method to show hyperplastic nodules of liver tissue surrounded by bands of fibrous tissue (x 5·5).

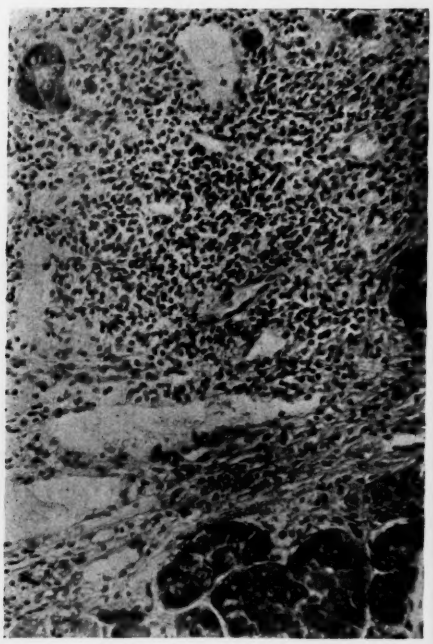
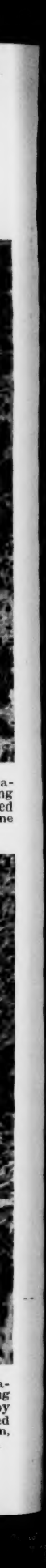


FIGURE XII. Case 21: chronic hepatitis; aspiration biopsy (25 weeks after onset) showing discrete nodules of liver cells surrounded by broad bands of connective tissue still infiltrated by inflammatory cells. (Best's carmine stain, x 164.)



in four of our patients (Cases 4, 7, 13 and 18), as they had received injections within five months of developing their jaundice.

For the sake of convenience all the patients in our series have been grouped together under the diagnosis of "infectious hepatitis".

THE PRESENT STUDY.

Selection of Cases.

The series includes twenty acute and twelve chronic cases. As was stated above, the duration of the illness in our series varied greatly, and although several typical acute cases have been included, it has been our endeavour to seek out patients who have been suffering from the chronic form of the disease. Most patients recover within three months, the usual duration being from four to eight weeks with complete recovery. We have placed in the "chronic" group those patients showing signs of active hepatitis for a period of more than four months.

There is accumulating experimental evidence that dietetic deficiency causes chronic hepatitis (Witts[32]). It appears that alcohol acts largely in this manner. Chemical poisons can also cause hepatitis. Himsworth and Glynn[33] discuss the effects of protein deficiency and describe "toxipathic" and "trophopathic" forms of hepatitis. The toxipathic group includes infectious hepatitis. In our series most of the patients in the chronic group were either children or young adults who had been in good health and taking a full, well-balanced diet rich in vitamins. With few exceptions (Cases 9 and 14) they had not been taking alcohol or drugs and their occupation had not exposed them to chemical toxins.

Method of Study.

The present series was studied by: (*a*) clinical observations, including history and physical examination; (*b*) biochemical tests of liver function and other relevant tests; (*c*) histological examination of the liver, the biopsy specimens being obtained either by aspiration biopsy or by exploratory laparotomy; (*d*) X-ray examination.

Clinical Observations.—Special note was made of the history of contact with other suspected sufferers from hepatitis. The possibility of other causes of hepatitis was also examined—that is, other infections, chemical and dietetic causes.

Biochemical Tests of Liver Function and other Relevant Tests.—A series of biochemical investigations was made on one 12-millilitre sample of blood, two millilitres being oxalated and serum being separated from the remaining ten millilitres. Tests were made on serum collected less than twelve hours previously. The following estimations were selected as the most efficient in detection of liver abnormality, and these were planned to give a comprehensive picture of liver function. Estimations of bilirubin content (quantitative Van den Bergh test), cephalin flocculation (Hangar[34]), alkaline phosphatase level (King and Armstrong[35]), total serum protein (Phillips *et alii*[36]), and the albumin-globulin ratio (Howe[37] modified by Hawk[38]) were made on the serum. With the use of the oral method an hippuric acid excretion test (Quick[39]) was performed on the same day that the blood sample was collected. Prothrombin estimations (Quick,[39] modified by Kark and Lozner[40]) were made before aspiration biopsy or operation. A blood urea determination (Maclean) and a urine examination for albumin and casts were made to detect impaired renal function. The serum amylase content (Winslow) was estimated to detect acute pancreatitis. To complete the investigation, a Wassermann test, a Casoni test, a hæmoglobin estimation and a blood film examination were made. Fractional gruel test meal examinations were usually carried out. Pepsin (Anson[41]) and chloride determinations were made, as well as the usual titrations for free and combined acidity. The response to histamine was determined in cases of achlorhydria, a standard dose of 0·3 milligramme being given and a sample of gastric contents removed forty-five minutes later and tested for free hydrochloric acid.

Histological Examination of the Liver.—Aspiration biopsy was made in seventeen of our cases. The biopsy studies of Roholm and Iversen[3] on cases of "catarrhal jaundice" threw much light on the histological changes which took place in the liver. Later, in London, further work in this field was undertaken by Sherlock[4][42] working with Dible, and by Davis *et alii*[43] in America. Recently two of us (W. E. King and J. W. Perry[44]) have described in detail the technique of liver biopsy which has been employed in the present series. Using the Franseen needle, they have performed biopsies in nine acute and eight chronic cases. No serious complications were encountered. One patient (Case 14) showed signs of minor intraperitoneal hæmorrhage, manifested by generalized abdominal pains and some rigidity. There was no rise in pulse rate or fall in hæmoglobin value. He showed satisfactory improvement with rest and morphine. Material for histological examination was obtained from three additional patients at operation.

Post-mortem examination was performed in the case of the four patients who died from hepatitis.

X-Ray Examination.—A plain X-ray examination of the chest and abdomen was made in all cases. Cholecystography was used in selected cases when the jaundice had cleared.

Group I: Acute Infectious Hepatitis.

The present study has shown that a limited number of classical acute cases of infectious hepatitis of short duration was occurring in the community. The series included twenty typical cases of moderate to mild severity and one case of subacute hepatic necrosis which ended fatally (Case 9). No case of mild acute infectious hepatitis without clinical jaundice was detected, but no systematic search was made amongst contacts.

Clinical Features of Acute Infectious Hepatitis.

The classical moderate to mild cases of acute infectious hepatitis began with upper abdominal pain, nausea, vomiting and pyrexia. After a few days jaundice appeared, the urine became dark, and the stools light in colour. The liver was enlarged and tender and the spleen often became palpable and tender. The illness lasted for one or two months and was followed by complete recovery. This was by far the commonest form of the disease.

A comprehensive study of the cytology of the blood was not usually made. Havens and Marck[45] found that in infected volunteers there was a fall in the numbers of lymphocytes and of polymorphonuclear cells with the onset of pyrexia. Usually this was followed a day or so later by lymphocytosis, and often atypical lymphocytes appeared, such as are seen in infectious mononucleosis. With the appearance of jaundice the white cell count usually returned to normal.

The following case is typical of this acute group.

CASE I.—P.A., a female patient, aged nineteen years, was admitted to the Royal Melbourne Hospital on October 25, 1946. Five days before her admission she had suffered from shivering, discomfort in the upper part of the abdomen and vomiting. Two days later jaundice appeared, the urine was dark and the stools were light in colour. She was not severely ill, the liver was palpable two fingers' breadth below the costal margin and a low-grade fever lasted for three days. Biochemical tests were made. The serum bilirubin content was raised (six units), urobilin was present in the urine, hippuric acid excretion was impaired (2·1 grammes), and the result of the cephalin flocculation test was strongly positive. The other tests all gave negative results.

Two weeks later the jaundice had cleared, the cephalin flocculation test gave a negative result and her condition appeared to be greatly improved, but she was still weak. Her subsequent progress was quite satisfactory.

This was a typical mild attack of hepatitis with complete recovery. The rapid improvement in the result of the cephalin flocculation test is of interest.

In the fulminating group must be included a fatal case (Case 9), that of a patient who developed severe hepatitis with increasing jaundice, drowsiness, mental confusion and itchiness of the skin. The fæces were clay-coloured, and the liver, at first enlarged, later became impalpable. The patient died seven weeks after the onset from "subacute hepatic necrosis". These cases of acute or subacute hepatic necrosis are rare. They have been studied by

TABLE I.

A Summary of the Investigation of Twenty Acute and Twelve Chronic Cases of Hepatitis.

Case Number, Patient's Initials.	Age. (Yrs.)	Duration. (Weeks.)	Date.	Liver. (Centimetres below Costal Margin.)	Spleen. (Centimetres below Costal Margin.)	Serum Bilirubin. (Normal, 0·2 to 1·0.)	Bile in Urine. (Normal, nil.)	Urobilin in Urine. (Normal, less than 20.)[1]	Hippuric Acid Excretion. (Normal, 3 or More Grms.)[2]	Cephalin Flocculation, 24 hours. (Normal, nil.)	Total Serum Protein Content. (Normal, 6·0 to 8·5 Grms. *per Centum*.)	Serum Albumin. (Normal, 3·5 to 5·2 Grms. *per Centum*.)	Serum Globulin. (Normal, 2·0 to 3·5 Grms. *per Centum*.)	Albumin-Globulin. Ratio. (Normal, 4 : 1 to 1·2 : 1.)	Prothrombin Index. (Normal, over 80%.)	Alkaline Phosphatase (Normal, 3 to 13 Units.)	Test Meal Free Acid, Maximum. (Normal, 60.)	Comments.
									Acute Hepatitis.									
I. P.A.	19	1 2	29/10/46 5/11/46	4 —	0 —	6·0 1·0	+ —	100 —	2·1 —	+++ Nil	7·7 —	5·5 —	2·2 —	2·5 —	114 —	25 —	Nil —	Mild course. Recovery. Possibly homologous serum jaundice.
II. P.B.	26	1 3 5	20/ 5/47 4/ 6/47 18/ 6/47	4 — —	2 — —	25·0 10·0 1·0	+++ 0 —	20 10 —	1·0 0·8 1·4	+++ ++ Nil	7·3 — 6·8	5·0 — 5·0	2·3 — 1·8	2·1 — 2·8	85 — —	19 15 —	— — —	Acute attack with recovery. Had intramuscular injection four months earlier.
III. F.C.	20	2 17 29	12/ 7/46 29/10/46 23/ 1/47	2 — —	0 — —	0·5 0·2 0·2	Trace — —	10 — —	2·97 — —	+++ +++ Nil	8·3 8·1 7·2	5·05 4·5 5·5	3·25 3·6 1·7	1·5 1·25 3·2	— — —	— — —	— — —	Mild course. Rapid clinical improvement.
IV. B.C.	45	36	27/ 5/46	0	0	0·2	Nil	1	3·5	Nil	6·3	—	—	—	95	—	27	Short acute attack four months previously with recovery. (See case report.)
V. L.D.	30	1 3 4	4/ 2/47 18/ 2/47 25/ 2/47	6 — —	2 — —	2·5 1·0 0·7	— — —	10 — —	— 2·4 —	+ Nil Nil	7·2 — 7·1	4·3 — 4·5	2·9 — 2·6	1·5 — 1·9	100 — —	17 — —	35 — —	Moderately severe attack. Followed by psychosis with recovery. Biopsy: acute hepatitis.
VI. K.D.	8	2	13/ 2/47	4	0	0·5	—	—	—	+++	7·0	5·2	1·8	2·8	—	34	—	Mild. Recovery.
VII. W.D.			10/12/46	4	0	4·3	++	—	—	—	7·6	4·6	3·0	1·5	—	8	—	Jaundice three weeks after blood transfusion. Biopsy: acute hepatitis. Ill three months. Complete recovery.
VIII. P.D.	13	16 21	21/ 1/47 25/ 2/47 19/ 6/47	6 —	0 —	2·5 0·3 1·2	+ Nil Nil	40 1 Nil	1·8[3] 2·7[3] 2·98[3]	++ Trace Nil	7·9 7·3 6·8	4·15 4·7 4·8	3·75 2·6 2·0	1·1 1·8 2·4	109 — —	25 15 16	— — —	Typical acute attack. History of contact. Recovery.
IX. A.D.	48	3 7	16/ 9/46 11/10/46	6 —	0 —	13·6 19·0	+++ +++	Not increased —	1·49 —	+++ +++	5·4 —	2·7 —	2·7 —	1·0 —	60 —	30 —	— —	Severe fatal illness. Chronic alcoholic. Died after laparotomy. (See case report.)
X. F.D.	10	3	13/ 2/47	4	2	3·5	—	—	—	+++	7·0	3·6	3·4	1·05	—	33	—	Typical mild acute attack. Complete recovery. Ill one month.
XI. F.E.	47	3 7	20/ 5/47 19/ 6/47	4 —	2 —	33·0 3·0	+++ —	40 —	3·5 —	+ 0	6·5 —	4·3 —	2·2 —	1·9 —	85 —	23 —	40 —	Acute attack with recovery. (See case report.)
XII. N.G.	36	2 4	25/11/46 10/12/46	2 —	0 —	10·0 0·7	++ —	Not increased —	2·2 —	++ Nil	6·8 —	5·2 —	1·6 —	3·2 —	84 —	24 —	60 —	Typical acute attack. Recovery.
XIII. F.H.	39	2 2 4	28/ 5/46 1/ 6/46 13/ 6/46	6 — —	2 — —	6·0 5·0 1·2	+ — —	10 — —	2·92 — —	++ ++ Nil	6·4 — —	— — —	— — —	— — —	94 — —	— — —	— — —	Typical acute attack. Recovery. Had previous injection.
XIV. G.H.	30	3 6	3/ 3/47 25/ 3/47	4 —	0 —	62·0 2·5	+++ Nil	Nil 100	1·5 1·7	Nil +++	6·4 7·5	4·6 4·8	1·8 2·7	2·5 1·8	87 —	25 36	45 —	Acute attack with recovery. (See case report.)
XV. A.M.	30	1 3	14/ 5/47 29/ 5/47	4 —	0 0	33·0 0·5	++ —	Nil —	1·4 —	+++ Nil	6·5 —	3·5 —	3·0 —	1·2 —	80 —	22 —	15 —	Acute attack with recovery.
XVI. A.N.	17	7 12 14	20/ 8/46 26/ 9/46 8/10/46	2 — —	0 — —	20·0 5·0 1·0	+ — —	Not increased — —	3·5 — —	Nil Nil Nil	6·1 7·5 —	4·1 5·5 —	2·0 2·0 —	2·05 2·7 —	68 — —	26 — —	20 — —	Typical acute attack. Recovery. History of contact. Biopsy: acute hepatitis.
XVII. C.P.	33	1 2	29/ 4/47 6/ 5/47	4 —	0 —	33·0 12·5	++ —	Nil —	2·4 —	+++ Nil	5·4 —	3·6 —	1·8 —	2·0 —	84 —	22 —	20 —	Acute attack with recovery.
XVIII. W.P.	22	2 5 7	11/ 6/46 2/ 7/46 12/ 7/46	2 — —	0 — —	30·0 6·4 2·5	++ ++ —	20 — —	1·34 — —	+++ + Nil	6·3 — —	4·45 — —	1·85 — —	2·4 — —	— — —	18 — —	39 — —	Mild attack. Recovery. Had previous injections.

[1] Urobilin in urine: The figures refer to the highest dilution of urine which gives a pink colour with Ehlich's reagent (Wallace and Diamond).

[2] The normal excretion of hippuric acid in four hours is three or more grammes (expressed as benzoic acid) after a test dose of six grammes of sodium benzoate. In the cases indicated the patients were not fully grown and four grammes of sodium benzoate were given. Two grammes of hippuric acid would therefore be the normal amount excreted.

TABLE I.—*Continued.*

[1] Urobilin in urine: The figures refer to the highest dilution of urine which gives a pink colour with Ehlich's reagent (Wallace and Diamond).
[2] The normal excretion of hippuric acid in four hours is three or more grammes (expressed as benzoic acid) after a test dose of six grammes of sodium benzoate. In the cases indicated the patients were not fully grown and four grammes of sodium benzoate were given. Two grammes of hippuric acid would therefore be the normal amount excreted.

TABLE I.—*Continued.*

A Summary of the Investigation of Twenty Acute and Twelve Chronic Cases of Hepatitis.—Continued.

Case Number, Patient's Initials.	Age. (Yrs.)	Duration. (Weeks.)	Date.	Liver. (Centimetres below Costal Margin.)	Spleen. (Centimetres below Costal Margin.)	Serum Bilirubin. (Normal, 0·2 to 1·0.)	Bile in Urine. (Normal, nil.)	Urobilin in Urine. (Normal, less than 20.)[1]	Hippuric Acid Excretion. (Normal, 3 or More Grms.)[2]	Cephalin Flocculation, 24 hours. (Normal, nil.)	Total Serum Protein Content. (Normal, 6·0 to 8·5 Grms. *per Centum.*)	Serum Albumin. (Normal, 3·5 to 5·2 Grms. *per Centum.*)	Serum Globulin. (Normal, 2·0 to 3·5 Grms. *per Centum.*)	Albumin-Globulin Ratio. (Normal, 4 : 1 to 1·2 : 1.)	Prothrombin Index. (Normal, over 80%.)	Alkaline Phosphatase (Normal, 3 to 13 Units.)	Test Meal Free Acid, Maximum. (Normal, 60.)	Comments.
XIX. E.S.	46	1	24/10/46	4	4	20·0	++	Not increased	1·3	+	5·7	4·2	1·5	2·8	80	17	22	Typical acute attack. Recovery. (See case report.) Biopsy: acute hepatitis.
		2	1/11/46	—	—	30·0	—	—	—	Nil	—	—	—	—	—	—	—	
		9	24/12/46	—	—	1·0	—	—	2·3	Nil	—	—	—	—	—	—	—	
XX. R.S.	25	2	3/ 3/47	4	4	0·3	Nil	200	2·2	+++	7·0	4·1	2·9	1·4	105	16·5	10	Acute attack. Jaundice subsided on admission. Recovery.
		4	19/ 3/47	—	—	0·5	Nil	10	1·8	+	—	—	—	—	—	—	—	
										Chronic Hepatitis.								
XXI. A.G.	57	2	20/12/46	4	2	15·0	++	—	0·53	+++	6·8	3·05	3·75	0·81	63	37	55	Classical acute attack. Became chronic. Slow improvement. (See case report.)
		5	9/ 1/47	—	—	10·0	—	—	—	+++	6·2	2·55	3·65	0·69	—	—	—	
		13	5/ 3/47	—	—	2·0	—	10	—	+++	7·0	2·85	4·15	0·68	—	—	—	
		24	20/ 5/47	—	—	1·0	Nil	20	0·9	+++	7·0	4·1	2·9	1·4	76	20	—	
XXII. P.C.	19	3	20/ 8/46	2	0	29·0	+++	10	1·3	+++	7·2	3·5	3·7	0·94	83	12	38	Onset with acute attack. Biopsies: chronic hepatitis. Progressive lesion. Fatal.
		8	24/ 9/46	—	—	3·8	—	—	—	+++	7·0	3·9	3·1	1·26	—	—	—	
		30	27/ 2/47	—	—	6·5	—	—	—	+++	8·2	3·6	4·6	0·78	—	—	—	
		41	13/ 5/47	—	—	12·5	—	—	—	+++	8·1	2·7	5·4	0·5	—	—	—	
		44	6/ 6/47	—	—	40·0	—	—	—	+++	6·6	2·2	4·4	0·5	—	11	—	
XXIII. F.D.	28	20	10/ 7/46	6	4	10·0	—	—	—	++	4·2	1·75	2·45	0·71	—	16	—	Army case—onset, New Britain. Fatal. *Post mortem*: typical subacute hepatitis, necrosis and nodular hyperplasia.
XXIV. P.F.	20	30	7/ 6/46	2	2	24·0	+++	20	0·95	+++	7·7	2·9	4·8	0·60	63	—	47	Onset with typical acute attack. Chronic, with relapses; improvement after two years. (See case report.)
		37	24/ 7/46	—	—	12·5	—	—	—	+++	6·8	2·8	4·0	0·70	—	—	—	
		64	28/ 1/47	—	—	3·0	—	—	—	+++	7·2	4·3	2·9	1·4	—	24	—	
		79	15/ 5/47	—	—	1·5	—	—	1·4	++	7·6	3·2	4·4	0·7	—	22	—	
XXV. F.G.	27	44	24/12/46	2	2	0·8	Nil	10	0·73	+++	8·2	—	—	—	96	—	—	Onset with purpura. Jaundice three months later. Chronic course. (See case report.)
		63	6/ 5/47	—	—	27·0	+++	Not increased	1·5	+++	9·7	3·0	6·7	0·45	82	26	—	
XXVI. M.H.	18	68	22/10/46	2	0	0·5	—	1	2·2	+++	8·25	3·5	4·75	0·73	—	—	Nil	Onset with acute attack. Chronic course with relapses. (See case report.)
		72	19/11/46	—	—	1·0	—	—	—	++	7·9	4·3	3·6	1·2	—	23·5	—	
		82	28/ 1/47	—	—	2·0	—	—	—	+++	7·3	2·95	4·35	0·67	82	16	—	
		101	10/ 6/47	—	—	1·0	Nil	1	1·63	+++	8·5	3·4	5·1	0·67	—	17·5	—	
XXVII. E.H.	47	72	18/ 7/46	6	0	25·0	+	10	—	+++	6·8	4·1	2·7	1·5	82	18	56	Onset: typical acute attack. Chronic course with relapses. Slow improvement. (See case report.)
		81	20/ 9/46	—	—	0·2	—	—	—	+	7·1	4·45	2·65	1·7	—	28	—	
		103	25/ 2/47	—	—	0·2	Nil	1	2·5	Nil	7·3	4·45	2·85	1·5	—	16	—	
XXVIII N.K.I	30	28	13/ 2/47	2	8	1·0	+	1	1·2	+++	6·0	3·8	2·2	1·7	—	28	—	Acute onset. Chronic course. Fatal. (See case report.)
XXIX. A.M.	33	36	7/10/46	0	2	5·0	—	—	3·0	+	8·4	—	—	—	—	—	—	Acute onset. Chronic course. (See case report.)
		49	6/ 1/47	—	—	—	—	—	—	+++	—	—	—	—	—	—	—	
		58	7/ 3/47	—	—	10·0	—	—	1·1	+++	—	—						
XXX. L.R.	20	32	13/ 1/47	2	0	2·4	++	—	0·42	+++	5·8	2·7	3·1	0·87	—	58·5	—	Acute onset. Chronic course. Fatal. Biopsy: chronic hepatitis confirmed by post-mortem examination.
XXXI. D.S.	13	48	4/ 2/47	2	2	4·5	++	40	1·48	+++	8·6	3·05	4·55	0·67	68	22	—	Onset with oral hæmorrhages. Chronic course. (See case report.)
		53	13/ 3/47	—	—	7·0	—	—	—	+++	—	—	—	—	—	—	—	
		66	12/ 6/47	—	—	10·0	—	—	—	+++	8·1	2·5	5·6	0·44	77	—	—	
		68	24/ 6/47	—	—	5·0	—	—	—	+++	7·5	2·5	5·0	0·5	78	—	—	
XXXII. M.S.	15	16	17/12/46	6	2	2·0	+	10	0·31	+++	9·1	4·1	5·0	0·82	83	15	—	Acute onset. Chronic course with relapses. Biopsy: chronic hepatitis.

[1] Urobilin in urine: The figures refer to the highest dilution of urine which gives a pink colour with Ehrlich's reagent (Wallace and Diamond).
[2] The normal excretion of hippuric acid in four hours is three or more grammes (expressed as benzoic acid) after a test dose of six grammes of sodium benzoate. In the cases indicated the patients were not fully grown and four grammes of sodium benzoate were given. Two grammes of hippuric acid would therefore be the normal amount excreted.

Watson and Hoffbauer,[11] by Lucke[10][31] and by Fearnley.[46] Some of the patients die in the acute phase and some pass into a state of chronic ill health with remissions, as will be described in Group II. Others make a complete clinical recovery, but are left with latent liver damage which may later manifest itself as cirrhosis.

Biochemical Changes in Acute Infectious Hepatitis.

During the acute phase of the illness, the biochemical findings in our series were similar to those recorded by other workers in England, America and Australia (Rapoport,[47] Sherlock,[48] Maizels,[49] Higgins[30] and Corkill *et alii*[31]) (see Figure I). The serum bilirubin content was elevated (10 to 60 units), the urine contained bile pigment and salts, urobilin was detected in the urine in dilutions of 1 in 20 or more, depending on the stage of the disease. The hippuric acid test revealed diminished excretion, the result of the cephalin flocculation test was strongly positive, the total protein content remained within normal limits, and the albumin-globulin ratio was not

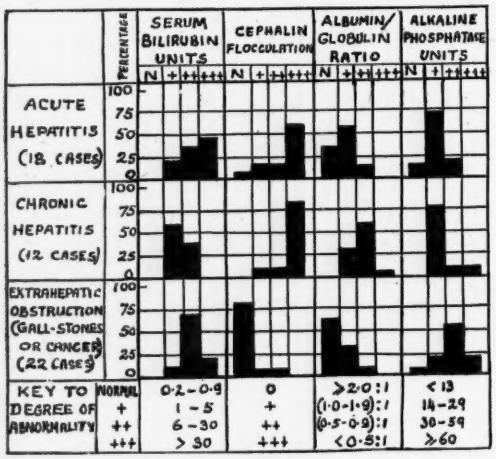


FIGURE I.

Showing the results of biochemical tests on patients suffering from jaundice. It will be noted that the cephalin flocculation test was the most informative single test in differentiating the cases of hepatitis from the cases of jaundice due to external obstruction.

usually reversed. It is worthy of note that of the three patients with acute hepatitis who showed the most pronounced change in the albumin-globulin ratio, two died and the condition of the other one became chronic (Cases 9, 22 and 21). The prothrombin index was sometimes diminished and often was slow to respond to parenterally administered vitamin *K*. The alkaline phosphatase content remained within normal limits or was moderately elevated. The blood urea content, the serum amylase content and the fractional test meal findings were usually within normal limits. Clinical improvement was accompanied by a definite improvement in biochemical findings.

The cephalin flocculation test proved to be the most informative single test in the acute cases, but its result was not invariably positive. In fourteen out of eighteen cases tested a "++" or stronger flocculation was present in twenty-four hours. In one other a strongly positive flocculation developed in forty-eight hours.

In Case 16 the patient, who had been in close contact with other patients suffering from typical infectious hepatitis, did not give a positive result to the cephalin flocculation test, although his clinical condition resembled infectious hepatitis. However, the test was not carried out till the eighth week of the disease. It is noteworthy that he was the only patient who also gave a normal response to the hippuric acid excretion test. On the other hand, there was one instance of late development of a positive response to the cephalin flocculation test (Case 14), the result becoming positive in the seventh week of the disease. The serum globulin fraction increased at the same time. In one acute case (Case 3) the result of the cephalin flocculation test remained positive for five months after apparent clinical recovery and the return of the results of the other tests to normal. As a rule, however, the continuance of abnormal biochemical findings should be viewed with some concern, especially if they are associated with prolonged debility, pain over the liver or slight jaundice.

The cephalin flocculation test is the most valuable test in differentiating between jaundice due to extrahepatic obstruction and jaundice due to diffuse hepatitis. The test is not specific for infectious hepatitis, as positive results may sometimes be obtained in other conditions, particularly other types of chronic hepatitis and virus infections.

Recently the serum proteins in cases of infectious hepatitis have been studied in America by electrophoresis and use of the method of Tiselius, and a fairly constant pattern has been obtained. Martin[32] has shown that this pattern is not specific for infectious hepatitis, as similar results have been given by the serum in cases of infectious mononucleosis and *lupus erythematosus*.

Pathological Changes in the Liver in Acute Infectious Hepatitis.

We have not had the opportunity of studying material from early mild acute cases, the commonest form of the disease, in which focal liver cell damage occurs about the region of the central vein and perhaps the portal canals. This type of lesion has been described by Cameron[6] and is summarized as a mild focal degeneration of liver cells, associated with an inflammatory cellular reaction and connective tissue increase. It is probable that all these changes are reversible, even the excess connective tissue diminishing or disappearing. The biopsy in Case 4, made five months after an acute attack of hepatitis, showed a normal liver. This was probably a case of homologous serum jaundice.

Massive cellular necrosis known as "acute yellow atrophy" and the less severe but more prolonged type known as "subacute yellow atrophy" are well recognized but rare forms of infectious hepatitis. In the case of "subacute yellow atrophy" (Case 9) there was extensive patchy destruction of liver cells and some invasion of portal canals and intracellular zones with inflammatory cells. There was commencing fibrosis in these areas. The liver damage led to death of the patient. Should a patient in this group survive, the further changes would consist of hyperplasia of the surviving cells, fibrosis and probably further damage of liver cells. Bile duct proliferation is variable. When hyperplasia is the predominant feature, a picture commonly referred to as healed subacute yellow atrophy or multiple nodular hyperplasia results. This stage may last for months or years and is discussed with the next group of cases.

The following four cases (Cases 4, 14, 19 and 9) represent increasing degrees of severity of the acute form of infectious hepatitis.

CASE 4.—B.C., a female patient, aged forty-five years, was admitted to hospital on June 20, 1946. Six months before admission she had been given malaria therapy and arsenical injections for cerebro-vascular syphilis. After thirteen intravenous injections of arsenic at weekly intervals she developed jaundice which lasted for two weeks. This was associated with epigastric discomfort, dark urine and clay-coloured stools. Four months before her admission to hospital she recovered. The patient was referred to the unit, as the physician in charge wished to give further injections of arsenic if clinical recovery was confirmed by biochemical tests and biopsy. The clinical examination and biochemical findings were within normal limits.

Biopsy revealed normal architecture. There was a slight increase of fibrous tissue in portal tracts, and a slight accumulation of inflammatory cells was present in this area.

Comment.—This had been a mild case of hepatitis, possibly due to the virus of homologous serum jaundice. The minimal changes in the liver indicated satisfactory resolution of the hepatitis. It was thought unlikely that the

changes in the liver were due to syphilis. The patient was subsequently given a course of penicillin treatment for her neuro-vascular syphilis.

CASE 14.—G.H., a male patient, aged thirty years, was admitted to the Royal Melbourne Hospital on March 2, 1947, with a five weeks' history of increasing painless jaundice with dark urine and pale stools. Moderate pruritus was present. On examination the patient was jaundiced, the liver was palpable two fingers' breadth below the costal margin and slightly tender, but the spleen was not palpable.

Biochemical tests (see Figure II) gave the following results. The serum bilirubin level was very high (62 units), bile salts and pigment were present in the urine, but no urobilin was detected. Hippuric acid excretion was impaired (1·5 grammes), the cephalin flocculation test produced a negative result, and the alkaline phosphatase level was moderately raised (25 units). The prothrombin index (87%), the total serum protein content and the albumin-globulin ratio were within normal limits.

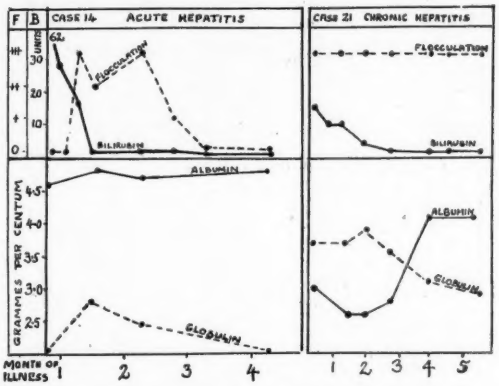


FIGURE II.

This shows the decline in serum bilirubin and cephalin flocculation in a case of acute infectious hepatitis of average severity with clinical recovery (Case 14, a male patient, aged thirty years). The albumin-globulin ratio was not disturbed. The chronic case (Case 21, a male patient, aged thirty-seven years) was of moderate severity, the onset being with ascites and enlargement of the liver and spleen. There was low-grade jaundice, the result of the cephalin flocculation test remained positive, and the albumin-globulin ratio was reversed. Two aspiration biopsies revealed extensive and progressive damage of the liver (see case report and Figures XI and XII). Clinical improvement was observed in the fifth month.

Liver biopsy was carried out on the fortieth day (see Figure VII). Microscopic examination of the section revealed a considerable disturbance of normal hepatic architecture. Many of the liver cells showed hyperplastic changes, and invasion of the portal tracts and liver lobules with inflammatory cells was a feature. Differential staining confirmed the presence of increased fibrous tissue in the portal tract regions, but it did not appear to have invaded the liver lobules. The findings were those of acute hepatitis in which there was some recovery with regeneration of liver cells, but an inflammatory reaction was still present.

By the eighth week of the illness the jaundice had decreased, the serum bilirubin content now being 17 units. The urine contained less bile pigment, and urobilin was not present. The cephalin flocculation test now produced a strongly positive result for the first time. The patient made an uninterrupted recovery. Fourteen weeks after the onset the serum bilirubin content had fallen (one unit), the cephalin flocculation test produced a negative result, and the hippuric acid excretion had improved (2·4 grammes).

Comment.—This was a severe case of infectious hepatitis with pronounced jaundice in the early stages. It is noteworthy that the cephalin flocculation test did not produce a positive result until the eighth week.

CASE 19.—E.S., a female patient, aged forty-six years, was admitted to the Royal Melbourne Hospital on October 23, 1946. The illness had begun two weeks previously with shivers, pyrexia and malaise, followed by epigastric discomfort and vomiting. One week later jaundice, dark urine and pale stools were observed. Examination revealed jaundice and a palpable liver and spleen.

Biochemical tests gave the following findings. The serum bilirubin level was elevated (20 to 45 units) for three weeks and then fell rapidly. The cephalin flocculation test produced a weakly positive result. Hippuric acid excretion was low (1·7 grammes), and two months later approached normal (2·3 grammes). Alkaline phosphatase content was only slightly increased (17 units).

Liver biopsy on the nineteenth day revealed only slightly disturbed architecture. The outstanding feature was infiltration of portal tracts with macrophages, round cells, fibroblasts and a few polymorphonuclear cells. There was slight hyperplasia of bile ducts, and a few inflammatory cells, consisting of round cells and fibroblasts, extended between the liver cells. No excess pigment was present.

For three weeks the patient remained moderately ill, with jaundice, clay-coloured stools and a temperature elevated to 99° to 100° F. She then progressively and completely recovered. Four weeks later a cholecystogram showed normal appearances. When the patient was examined four months later she was very well indeed.

Comment.—This patient caused some anxiety, as it seemed possible that a stone might be present in the common duct, since the cephalin flocculation test produced only a weakly positive result. However, the low alkaline phosphatase level, the palpable spleen and the findings on aspiration biopsy did not favour extrahepatic obstruction, and operation was avoided.

CASE 9.—A.D., a male patient, aged forty-eight years, was admitted to the Royal Melbourne Hospital on October 12, 1946, and died four weeks later from subacute necrosis of the liver. This patient had admitted to taking six pints of beer a day; but his landlady stated that he indulged in periodic bouts of alcoholic excess, during which he consumed a variety of spirits and wines. However, in spite of this, he claimed that he was in good health and was taking a full, well-balanced diet until three weeks prior to his admission to hospital, when suddenly he developed pain in the upper part of the abdomen and in the shoulders. This was followed by vomiting. During the next two days he had a nagging pain in the right upper quadrant of the abdomen and jaundice appeared, with the passage of dark urine and clay-coloured stools. His skin was itchy. At first he appeared only moderately ill; jaundice was pronounced and the liver was palpable three fingers' breadth below the costal margin.

The intense and increasing jaundice (13 to 37 units of bilirubin), the impaired hippuric acid excretion (1·5 grammes), the strong positive result to the cephalin flocculation test, the fall in albumin-globulin ratio (1·0), and the intermediate rise in alkaline phosphatase (30 units), all suggested hepatitis rather than extrahepatic obstruction. Finally, the low prothrombin index with failure to respond to intense vitamin *K* therapy was also in favour of diffuse hepatitis.

During the next four weeks he gradually became worse with increasing drowsiness. He had no pyrexia in hospital, although he considered that he was "shivery and hot" prior to his admission. The liver slowly diminished in size until it was no longer palpable. Three weeks after his admission to hospital his abdomen was explored under local anæsthesia, as his condition was becoming worse and it was feared that a stone might be blocking the common bile duct. At operation the liver was seen to be dark, bile-stained and nodular. The common bile duct was not dilated and did not contain stones. The gall-bladder was normal. After the operation his drowsiness increased, and he became delirious and finally lapsed into coma. He died nine days after operation, in the seventh week of his illness. Intravenous infusions of glucose and saline solution produced some temporary improvement in his condition. No casein hydrolysate was available. A blood transfusion was given prior to operation, as the prothrombin index was low and could not be elevated by injections of vitamin *K*. Hæmorrhage was easily controlled at operation.

Post-Mortem Examination.

At the post-mortem examination (see Figures IV and V) the liver was seen to be greatly shrunken (weight 36 ounces) and greyish in colour, and to have a wrinkled, opaque capsule. In the cut surface of the liver an irregular pattern of greenish-yellow nodules was seen, between which lay firm tissue resembling normal liver. The remainder of the autopsy revealed a normal heart, congested lungs, no abnormality in the peritoneal cavity, normal gall-bladder and bile ducts and a normal spleen.

Microscopic examination of the liver revealed complete loss of normal liver architecture. Only a few isolated areas

of liver cells were seen, in which multinucleate forms and irregularity of cell shape were suggestive of hyperplasia. The bulk of the tissue consisted of a stroma of fine collagenous connective tissue, in which were seen thin-walled blood vessels and numerous cells. The cells included lymphocytes, young fibroblasts and mononuclear phagocytes. Polymorphonuclear cells were scanty. Occasional single liver cells were seen, and there was an apparent increase in bile duct elements. Granular bile pigment was present within phagocytes and lying free.

Comment.—In this case it is impossible to decide the relative parts played by alcoholism and infectious hepatitis. Either or both may have been culpable. In spite of his periodic alcoholic excesses, the patient appeared to be in good health until he was seized with the sudden illness with shivers, considerable pain over the liver and the other signs of severe hepatitis which rapidly increased in severity and became fatal. Biochemical findings and the post-mortem examination revealed severe hepatitis with necrosis. In the light of our subsequent experience it is considered that laparotomy could have been avoided in this case.

Group II: Chronic Infectious Hepatitis.

Clinical Features of Chronic Infectious Hepatitis.

As has been described previously, there are three grades of severity in acute infectious hepatitis: first, the large group of classical cases of moderate to mild severity lasting from four to eight weeks; secondly, the fulminating cases of acute and subacute necrosis; thirdly, the very mild cases without overt jaundice and often without definite symptoms of hepatitis, as reported by Paul.[9] Hepatitis from any one of these groups may fail to resolve and pass into the chronic phase with persistent inflammatory activity and nodular hyperplasia. As was stated previously, we have included in the "chronic" group all those patients showing signs of active hepatitis for more than four months. In the "chronic" group of twelve patients there are four whose illness first began with a classical acute attack, one whose disorder began with a severe illness with ascites, and seven who gave no definite history of any initial acute attack. In the last group, it is assumed that the initial infection was so mild that it failed to be diagnosed.

Some patients with acute infectious hepatitis, especially those in the "severe" group, had a protracted illness and so passed into the chronic phase, with prolonged jaundice, a tendency to hæmorrhage with anæmia, loss of energy and severe anorexia. The liver was enlarged and later became smaller; it was tender and gave rise to a chronic aching pain which sometimes became more severe, even resembling gall-stone colic. This happening was first described to us by the late Dr. Stewart Cowen. More commonly, the acute symptoms subsided after four to eight weeks; but convalescence was unsatisfactory. The patients continued to show mental and physical lassitude, lack of appetite and flatulent dyspepsia. They often became petulant and introspective. Sometimes an icteric tinge of the conjunctivæ or skin was apparent. Menstruation ceased in two cases (26 and 31).

The following case report describes this stage of chronic ill health.

CASE 26.—M.H., a female patient, aged eighteen years, was admitted to the Royal Melbourne Hospital on October 5, 1946, with the diagnosis of chronic hepatitis. Sixteen months previously she had suffered from upper abdominal pain with some vomiting and diarrhœa. Two weeks later she became jaundiced and passed dark urine and pale stools. The jaundice persisted for four months and then faded, to reappear occasionally for a few days. Strenuous exercise appeared to provoke the jaundice. During the exacerbations in the jaundice she had epigastric discomfort and passed loose offensive stools. Since the onset she had remained in chronic ill health, menstruation had ceased and she suffered from frequent epistaxis.

Examination revealed slight jaundice and general listlessness; the liver was enlarged to one finger's breadth below the costal margin.

Biochemical tests (see Figure III) produced typical findings of chronic hepatitis; slight jaundice was present (serum bilirubin two units), the cephalin flocculation test produced a strongly positive result, hippuric acid excretion was somewhat impaired (2·2 grammes), and the albumin-globulin ratio was reversed (0·7).

A biopsy examination was made in the nineteenth month. The outstanding feature of the section was the encirclement of large collections of liver cells by bands of densely cellular fibrous tissue. The liver cells stained well, but showed some evidence of hyperplasia. No bile pigment was present. The inflammatory cells which packed the fibrous tissue consisted of numerous polymorphonuclear cells, macrophages, some small round cells and very numerous fibroblasts. This cellular fibrous tissue could be seen invading the liver lobules. The bile ducts were prominent and were increased in number.

During the three months up to June, 1947, with a supervised diet she has slowly improved. She has become stronger and more energetic and menstruation has recommenced. The results of chemical tests (bilirubin, two units, and cephalin flocculation test result strongly positive) remain abnormal, but they are approaching normal limits. The liver is still enlarged and firm.

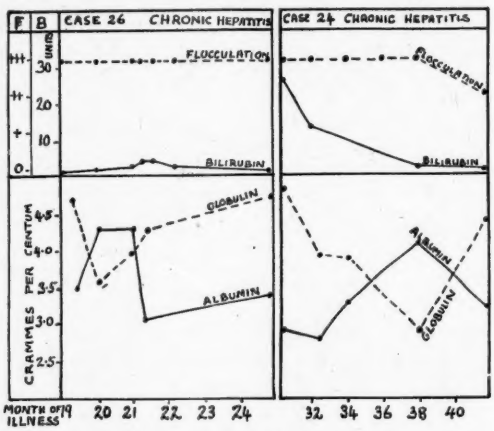


FIGURE III.

Cases 26 and 24, showing the biochemical changes in two young adult females suffering from chronic hepatitis. Both gave a history of chronic ill health with intermittent low-grade jaundice. Both patients showed persisting cephalin flocculation and reversal of the albumin-globulin ratio. Clinical improvement was evident towards the end of the test period.

Comment.—Twenty-three months ago a female patient, aged eighteen years, suffered from a typical attack of infectious hepatitis, and since then she has shown lack of energy, slight jaundice with exacerbations, and enlargement of the liver; biochemical tests have given typical results. Aspiration biopsy in the nineteenth month revealed chronic hepatitis. Recently there has been definite improvement in her general health and in the results of chemical tests.

From time to time in some cases the chronic infectious hepatitis relapsed, with return of the jaundice, low-grade fever, nausea and considerable disability. Several factors might play a part in provoking these exacerbations, especially respiratory infection, surgical operation, prolonged and excessive physical exertion, dietetic deficiency or the ingestion of alcohol. Some relapses were ushered in by a mild attack of diarrhœa, the stools being frequent, loose, pale and offensive (Cases 26, 25 and 24). The liver was usually enlarged, firm and tender. The spleen was palpable in eight of our twelve cases.

On occasions these relapses were severe, with moderate to deep jaundice, vomiting, drowsiness and ascites. Liver failure was always to be feared.

Chemical Tests in Chronic Infectious Hepatitis.

When these patients were subjected to biochemical tests, it was found that during relapses in their condition they had changes resembling those seen in patients suffering from their first acute attack of infectious hepatitis, with the exception that there was a more pronounced rise in

the serum globulin level with a fall in the albumin-globulin ratio. Moreover the prothrombin index was low and sometimes failed to respond to vitamin *K*. During remissions, when the patient was either "well" or more commonly suffering from mild ill health, the chemical tests usually revealed strong to moderate cephalin flocculation and a slight rise in the serum bilirubin level. Sometimes when the test results were inconclusive the history and the findings on aspiration biopsy were the only clues to the correct diagnosis (Case 27).

Pathological Changes in the Liver in Chronic Infectious Hepatitis.

Considerable disturbance of the normal liver architecture was common, and a variable picture was seen, caused by the haphazard distribution of areas of hyperplasia, connective tissue proliferation and liver cell degeneration. Cellular infiltration occurred most prominently in the connective tissue, but could also be seen in between the liver cells.

Our observations on the pathology of infectious hepatitis have left us with the impression that in the liver the fundamental process is a non-suppurative inflammation which may vary in its acute form, from mild liver cell damage capable of repair to massive fatal necrosis usually referred to as acute yellow atrophy. If the inflammatory process is prolonged, the subacute stage so clearly described by Hurley and Cameron[23] is reached in which repair and regeneration are occurring. The pathological descriptions "healed yellow atrophy" and "multiple nodular hyperplasia" refer to this stage. Chronic hepatitis with its intense scarring and nodularity is an end result of the process. The terms "Laennec's cirrhosis", "atrophic cirrhosis" or "hobnail liver" have been applied to this advanced state.

The following case report is of considerable interest, as the onset of the illness was severe, with deep jaundice, drowsiness and ascites, and aspiration biopsies were performed in the second and fifth months of the disease.

CASE 21.—A.G., a male Chinese, aged fifty-seven years, was first examined at the Royal Melbourne Hospital on December 17, 1946, and signs of activity were still present six months later. The diagnosis of chronic hepatitis was made. Two weeks prior to his admission to hospital he suffered from malaise, loss of appetite and weakness. One week later he became jaundiced, passing dark urine and pale stools. He had no acute pain. Examination revealed pronounced jaundice; the liver was enlarged to two fingers' breadth below the costal margin and the spleen was just palpable.

The results of biochemical tests are given in Figure II. The low hippuric acid excretion (0·53 gramme), the strongly positive response to the cephalin flocculation test, the intermediate rise in alkaline phosphatase level (36 units), and the low prothrombin index with failure to rise on the exhibition of vitamin *K* were all typical findings of moderately severe hepatitis.

The patient's condition slowly became worse, and he suffered from pronounced malaise and ascites. However, with prolonged rest, the performance of *paracentesis abdominis* and the giving of mercurial diuretics, he began to improve, and when discharged from hospital in the eleventh week of his illness he was much better but still weak. Slight ascites was present and the liver and spleen remained palpable and firm. The liver biopsy was carried out during a transfusion of fresh citrated blood, as the low prothrombin index could not be improved by vitamin *K* therapy. Six months after the onset his condition was much improved. No ascites was present, but the liver and spleen were still palpable and firm. The biochemical tests still revealed strong cephalin flocculation and impaired hippuric acid excretion (0·9 gramme), and the alkaline phosphatase level was only slightly elevated (20 units). However, the albumin-globulin ratio was restored to normal (1·4).

The findings on liver biopsy in the second month were as shown in Figure XI. The normal liver architecture was distorted, and lobules of liver tissue of varying size were seen to be intersected by bands of cellular fibrous tissue. The liver cells showed evidence of hyperplasia, but in other areas degeneration could be seen. There were small amounts of bile pigment to be seen in the liver cells, also between the cells. In places this pigment was contained in Kupffer cells. The inflammatory cells in the fibrous tissue consisted of polymorphonuclear cells, macrophages, small round cells and fibroblasts. The bile ducts were prominent.

A further liver biopsy was performed in the fifth month (see Figure XII). There had been considerable progress since the previous biopsy, and now there was almost complete disappearance of the normal liver architecture. Liver cells were collected into nodules, varying in size from large hyperplastic areas down to small collections of two or more cells. These nodules were surrounded by cellular connective tissue. Degenerative changes were minimal and no bile pigment could be seen.

Comment.—This was a severe case of infectious hepatitis with ascites, in which pronounced and typical chemical changes were present. Liver biopsies in the second and fifth months of the illness revealed progressive changes with evidence of repair. The clinical and biochemical findings also improved over this period.

Course of Chronic Infectious Hepatitis.

Patients in the "chronic" group suffered from varying degrees of disability for months, or sometimes for years. We have not had sufficient experience to entitle us to draw any significant conclusions. Our experience has led us to believe that in this group gradual improvement could often be expected (see Cases 24, 27, 21, 29 and 31). The attacks became less frequent and severe, the results of liver function tests improved, and although liver biopsy revealed gross changes in the architecture, there were considerable areas of hyperplasia. These hyperplastic areas were apparently able to function efficiently—a truly meritorious feat if one examined the tragic scenes of destruction which surrounded them. Moreover, there was less evidence of continuing activity, as was shown by the diminution in the numbers of inflammatory cells.

During the early months or years of their illness, these patients were adversely affected by intermittent infections, hæmorrhage, pregnancy or surgical operations. A full diet rich in methionine appeared to have a beneficial influence on the course. Prognosis could be assessed by continued clinical observation of the disease, repeated biochemical tests and aspiration biopsy.

In these chronic cases with relapses, a progressive destructive lesion in the liver appeared to be present. The cause of this progression is unknown. If it is a fact that the initial illness is due to the virus of either infectious hepatitis or homologous serum jaundice, then it may be reasonable to assume that this virus remains in the liver throughout the course of the disease, and that from time to time its activities are accelerated, causing a flare-up in the symptoms. On the other hand, it may be that the initial virus infection dies out, leaving a damaged liver which may continue to undergo progressive changes, due perhaps to the production of tissue-destroying antibodies provoked by the original infection. At any time the active destructive process may cease, and then any changes are in the direction of improvement. Much work remains to be done in this field.

This chronic form of the disease is illustrated by the following three case records (24, 27 and 28).

CASE 24.—P.F., a female patient, aged twenty years, was admitted to the Royal Melbourne Hospital on June 4, 1946. In January, 1944, her illness began with pallor and weakness. One month later she became jaundiced, passing dark urine and loose, pale stools. The jaundice was of only moderate severity, but it persisted with exacerbations and remissions until she was last examined in January, 1947. Six months after the onset laparotomy was performed because of severe right upper abdominal pain and increasing jaundice with clay-coloured stools. At operation the liver was found to be shrunken, and "practically the whole of the right lobe was studded with small, black nodules and the left lobe, except for its junction with the right lobe, appeared fairly normal". The gall-bladder and bile ducts were normal.

Examination of the biopsy specimen taken at operation showed that no normal liver architecture was visible. Liver tissue was not abundant and was comprised of several hyperplastic nodules in which were cells of varying size and shape, some containing multiple nuclei. Examination of these areas revealed bile pigmentation, both within cells and within bile canaliculi. The remainder of the tissue consisted of a collagenous stroma containing numerous cells mostly of the non-granular series, including lymphocytes in

aggregates, fibroblasts and phagocytes. Blood vessels were not numerous and those present were small and thin-walled. There were many small bile ducts, some containing deposits of bile pigment.

When the patient was first admitted to the clinical research unit in June, 1946 (two and a half years after the onset), her jaundice had relapsed after a mild attack of bronchitis. She was deeply jaundiced, her stools were pale, and her liver and spleen was both just palpable and very tender. She had a slight rise in temperature and a rapid pulse. One month later she was discharged from hospital, improved in health, but still slightly jaundiced.

Biochemical tests (see Figure III) gave the following results. When first admitted to the unit two and a half years after the onset, the patient was deeply jaundiced (24 units of serum bilirubin), the cephalin flocculation test produced a strongly positive result, hippuric acid excretion was impaired, the albumin-globulin ratio was reversed (0·6), there was an intermediate rise in the alkaline phosphatase level (47 units), and the prothrombin index was lowered (63%). During the following twelve months the chemical tests revealed slow but steady improvement. One year later (three and a half years after onset) the chemical tests revealed a slightly elevated bilirubin level (1·5 units), impaired hippuric acid excretion (1·4 grammes), an inverted albumin-globulin ratio (0·7), and only slightly elevated alkaline phosphatase level (22 units); the cephalin flocculation test produced a strongly positive result. The patient has shown slow improvement in her general health and well-being. The jaundice has cleared, but the liver and spleen are still easily palpable. She is now preparing to undertake light manual work.

Comment.—This female patient, aged twenty years, developed a classical attack of infectious hepatitis of moderate severity. The process failed to resolve and she remained in chronic ill health with varying degrees of jaundice for two and a half years. During the last twelve months she has shown distinct improvement and is now preparing to undertake light manual work. Examination of a liver biopsy specimen taken at operation six months after the onset revealed chronic hepatitis. During the past twelve months chemical tests have constantly shown the changes of infectious hepatitis, but there is definite improvement.

CASE 27.—E.H., a female patient, aged forty-seven years, was admitted to the clinical research unit on June 17, 1946, with the diagnosis of chronic hepatitis. Twenty-one months previously she had had a typical attack of acute infectious hepatitis with epigastric discomfort and nausea, followed by jaundice and the passage of dark urine and pale loose stools. She was ill in bed for five weeks and remained jaundiced for eight weeks. One month later she had a minor relapse, with return of the jaundice for a few days. Three months later (June, 1945) she suffered from a further attack with jaundice. Tenderness was present over the liver, and the spleen was just palpable. Cholecystography revealed no abnormality, the colloidal gold test produced a positive result, the albumin-globulin ratio was reversed and deep jaundice was present (serum bilirubin 30 units). Her illness was diagnosed by Dr. Leslie Hurley as subacute hepatitis. She had two further attacks, one a year and the next eighteen months after the onset. She then stated that she had been feeling very well indeed for the previous six months, but for two weeks she had been suffering from a typical relapse with lassitude and jaundice. Examination showed that the patient was deeply jaundiced, and a scattered erythematous rash was present on the trunk. The liver was enlarged to three fingers' breadth below the costal margin and the spleen was just palpable.

Biochemical tests revealed a high serum bilirubin level (25 units), strongly positive cephalin flocculation and impaired hippuric acid excretion (0·3 gramme).

Six months after the patient's discharge from hospital, the cephalin flocculation test produced a negative result and the albumin-globulin ratio was within normal limits. She remained in good health for ten months after her discharge from hospital, but the liver and spleen remained enlarged and firm.

A biopsy in the nineteenth month (July, 1946) revealed some distortion of liver architecture mainly in the region of the portal tracts, in which was evident increased cellularity with histiocytes, lymphocytes and numerous fibroblasts. There was bile duct proliferation with small collections of bile pigment in liver cells. Increase of connective tissue could be seen in the portal tracts penetrating between the liver cells. In one area liver cells were isolated from the lobules by strands of connective tissue.

Comment.—In this case a female patient, aged forty-seven years, became ill twenty-one months prior to her admission to hospital with a typical attack of acute infectious hepatitis. Since then she has suffered from four acute relapses. In the last of these she showed typical symptoms and signs, and the results of chemical tests and histological changes in the liver were also typical. Ten months after her last relapse the spleen was still palpable. The general trend in her chronic illness appeared to be one of improvement. She remained in good health for ten months after her discharge from hospital.

CASE 28.—N.K., a female patient, aged thirty years, was admitted to the Royal Melbourne Hospital on February 11 and died on February 17, 1947. The diagnosis of her illness was chronic hepatitis. The patient had enjoyed excellent health until seven months prior to her admission to hospital, when she had an attack of acute hepatitis with nausea, epigastric pain and jaundice, and the passage of dark urine and pale fæces. This acute attack lasted for three weeks, but recovery was incomplete. She was weak and depressed, and occasionally was noted to be faintly jaundiced. Two months prior to her admission to hospital she had vomited blood and been admitted to the Royal Hobart Hospital, where it was noticed that she was pale, drowsy and weak. The liver and spleen were palpable, and marked ascites but no jaundice was present. Little improvement was brought about by mercurial diuretics, and she was later transferred to the Royal Melbourne Hospital. She was pale and weak, but not jaundiced. The abdomen was full with moderate ascites. The liver was only just palpable on inspiration. The spleen was enlarged to four fingers' breadth below the costal margin.

Biochemical tests were carried out. The serum bilirubin level was not elevated (1·0 unit), hippuric acid excretion was impaired (1·2 grammes), the cephalin flocculation test produced a strongly positive result, the albumin-globulin ratio was normal (1·7), the alkaline phosphatase level was moderately elevated (28 units), the hæmoglobin value was 70% and the urine was clear.

Two days after her admission to hospital the patient vomited blood, but was not in a severely collapsed state. However, during the next two days she became drowsy and lapsed into coma, showing no response to the infusion of glucose-saline solution or casein hydrolysate or to blood transfusion. She died six days after her admission to hospital. With the development of coma there was little change in the chemical findings; the serum bilirubin content was 1·2 units, while the blood urea level rose from 36 to 48 milligrammes *per centum*. Urobilin appeared in the urine. The cerebro-spinal fluid was clear.

A post-mortem examination was made (see Figures VIII, IX and X). The outstanding features were as follows. The œsophageal veins were dilated and tortuous, but no ulceration was seen. The liver was small and uniformly nodular, the cut surface showing a mosaic appearance with roughly circular areas of yellow liver substance separated by connective tissue. Microscopic examination revealed classical portal cirrhosis. There were large areas of liver cells surrounded by discrete areas of dense collagenous connective tissue containing a few non-granular cells and numerous small bile ducts. The spleen was large and smooth, and the splenic artery and vein were normal. Microscopic examination of sections of the spleen revealed loss of normal architecture, reduction in the number of Malpighian corpuscles and a great increase in fibrous tissue. In some areas young fibroblasts were invading homogeneous fibrin-like material, similar to that seen when a thrombus is organizing.

Comment.—In this case a female patient, aged thirty years, developed acute infectious hepatitis of mild severity, but the attack failed to resolve. During the next six months her health deteriorated and ascites appeared. Gastric hæmorrhages occurred on two occasions and were the precipitating cause of death. Jaundice was a feature of the initial attack, but subsequently was never pronounced. Post-mortem examination revealed portal cirrhosis, enlargement and fibrosis of the spleen, œsophageal varices and ascites.

TREATMENT OF ACUTE AND CHRONIC INFECTIOUS HEPATITIS.

During the early acute attack the patient should rest in bed until the acute symptoms have abated. He may then be allowed to sit out of bed for an hour or so during the day, but should be kept at rest until the jaundice

has subsided. It is wise, then, for the patient to have a peaceful holiday before returning to work. It will often be two to four months before he is fit to undertake physical exercise or be subjected to severe mental stress. Much work has been done to determine whether methionine helps during the early acute attack. This has recently been reviewed by Witts.[22] Hoagland and Shank[54] considered that the convalescence was not shortened by the use of methionine. In accordance with the work of Madden and Whipple,[55] it would appear to be wise to give the patient a diet rich in methionine-containing foods, such as milk, cheese, eggs and meat. During the acute phase the patients prefer carbohydrate foods, and this seems to be suitable and perhaps preferable so long as the protein intake is soon increased.

Should any operative procedure become essential, the prothrombin index should be estimated and vitamin *K* administered. If the index remains low, a transfusion of fresh blood should be given immediately before and after the operation.

In the severe cases in which life is threatened, all agree that the intravenous administration of glucose is of the greatest value. Encouraging evidence is now accumulating that the addition of protein hydrolysate to the glucose solution is of additional benefit.

Simon[56] describes a patient who was in coma for four days during the acute stage of infectious hepatitis. During the next six days he received 180 grammes of protein and 493 grammes of carbohydrate intravenously, and finally recovered.

Magee[57] has described two severe cases of homologous serum jaundice in which a most satisfactory response was obtained to the intravenous administration of protein hydrolysate in glucose and saline solution. To one patient he gave 1400 Calories, including 150 grammes of protein, intravenously each day.

In our series three cases of severe liver failure were encountered, and all ended fatally. In Case 9 the patient was treated with glucose and saline solution intravenously, but died seven weeks after the onset of the illness. He was intensely jaundiced and had been subjected to a laparotomy nine days prior to his death. In Case 28 the patient had been ill for seven months after a classical acute attack of infectious hepatitis. She lapsed into coma after a gastric hæmorrhage (probably losing one to two pints of blood) and showed no response to the intravenous administration of glucose and saline solution and of casein hydrolysate or to blood transfusion. The patient in Case 22 lapsed into coma after an upper respiratory tract infection. He showed no improvement on treatment with glucose and saline solution and with casein hydrolysate.

During the chronic stages of the disease our procedure is to give a special diet rich in methionine and to provide suitable occupation. Heavy manual work and strenuous sport have an adverse effect on the course of the disease, but light exercise to keep the patient occupied is recommended. It is unwise for the patient to become pregnant, especially when the relapses are common or severe, or when the biochemical tests and biopsy reveal liver deficiency and signs of activity. After the patient has remained well for two years, and the other findings, including biopsy, reveal no evidence of activity, then perhaps pregnancy may be permitted.

The following three cases (31, 29 and 25) also illustrate the variable nature and course of chronic infectious hepatitis.

CASE 31.—D.S., a female patient, aged thirteen years, was admitted to the Royal Melbourne Hospital on February 15, 1947, with the diagnosis of chronic hepatitis. One year prior to her admission to hospital she had suffered from excessive hæmorrhage after tooth extraction. Since then intermittent hæmorrhage had occurred. Three months prior to her admission to hospital she began to suffer from nausea, anorexia and jaundice. She improved after one week, but slight jaundice persisted, and she was depressed and easily fatigued. Her appetite was good and she gained in weight. The menses were regular prior to her tooth extraction, since when they had ceased.

Examination revealed mild jaundice, and the liver and spleen were palpable. A number of biochemical tests was carried out. The serum bilirubin level was elevated (4·5 units), hippuric acid excretion was impaired (1·5 grammes), the cephalin flocculation test produced a strongly positive reaction, the albumin-globulin ratio was reversed (0·7), and the alkaline phosphatase level was slightly elevated (22 units). The prothrombin index was lowered (68%) and failed to respond to the administration of vitamin *K*. When the patient was in hospital she suffered a mild relapse, the bilirubin level rising from 4·5 to 19 units. No liver biopsy was performed owing to the constantly impaired prothrombin index.

During the next six months her condition slowly improved; but she was still easily tired, slight jaundice was present and menstruation did not recommence. The results of biochemical tests remained abnormal; the serum bilirubin level was raised (2·5 units), the cephalin flocculation test produced a strongly positive reaction and the albumin-globulin ratio was reversed (0·7). The prothrombin index was 69%. She was given vitamin *K* intramuscularly and several carious teeth were removed without excessive hæmorrhage. A biopsy was then performed as a guide to treatment and prognosis. Examination of the specimen obtained by aspiration biopsy (seven months after the onset of jaundice) revealed complete disorganization of liver architecture. Nodules of liver cells were scattered at random and surrounded by cellular connective tissue containing numerous bile ducts, histiocytes, fibroblasts, round cells and a few polymorphonuclear cells. Bile pigment was present in small collections in liver cells and in phagocytes.

Comment.—The insidious onset of ill health in a young female, beginning with a hæmorrhagic tendency, debility and cessation of menstruation, suggests the possibility of a mild and unrecognized attack of infectious hepatitis. Liver disease was not apparent until nine months later, when jaundice first appeared and the liver and spleen were noticed to be enlarged. When the patient was admitted to hospital three months later, the results of biochemical tests were typical of infectious hepatitis. During the next four months she showed moderate improvement, but she was still weak and the results of biochemical tests were positive. Aspiration biopsy seven months after the onset of jaundice revealed the classical changes of active chronic infectious hepatitis.

CASE 29.—A.M., a married female patient, aged thirty-three years, was admitted to hospital on November 6, 1946, with the diagnosis of chronic hepatitis and early pregnancy. Three years prior to her admission to hospital she had suffered from an acute attack of infectious hepatitis, the jaundice lasting for one month. This was followed by ill health and dyspepsia. Seven months later the jaundice returned, and a laparotomy revealed nodularity of the liver with extensive perihepatitis and moderate enlargement of the spleen. Syphilitic hepatitis was considered, despite a negative response to the Wassermann test. The patient reacted adversely to arsenical treatment. During the next two years her condition slowly improved, but she was never completely well. When she was first investigated by the clinical research unit she was in the early months of her first pregnancy. This was terminated and sterilization was performed. After her discharge from hospital she showed signs of minor relapse, with jaundice and a positive response to the cephalin flocculation test. Biochemical tests on November 5, 1946, three years after the onset of her illness when she was admitted to hospital for termination of pregnancy, revealed slight jaundice (5·0 units), a weakly positive result to the cephalin flocculation test, impaired hippuric acid excretion (1·7 grammes), and reduction in the albumin-globulin ratio (1·0). Examination of a biopsy specimen taken at the time of the operation, November 6, revealed cellular infiltration, fibrosis and nodular hyperplasia.

Comment.—This case was one of chronic hepatitis following an acute attack three years previously. Liver biopsy made when pregnancy was terminated revealed chronic hepatitis with nodular hyperplasia.

CASE 25.—F.G., a male patient, aged twenty-seven years, was admitted to the Royal Melbourne Hospital on December 15, 1946, with the diagnosis of chronic hepatitis. For nine months prior to his admission to hospital he had had a recurrent purpuric rash on his legs. Three months after this he began to suffer from jaundice and debility. His urine was dark and his stools were clay-coloured. His liver and spleen were found to be enlarged. He had lost two stone in weight. Although the jaundice decreased after one month, it never cleared completely and his urine remained dark. The stools were normal in colour. During the week

prior to his admission to hospital he had pain over the liver and in the right shoulder.

On examination of the patient, no definite jaundice was apparent; the liver was enlarged to two fingers' breadth below the costal margin and the spleen was just palpable. There were signs of chronic right *otitis media*. Low-grade fever was present. Sulphonamides were administered for the *otitis media*. The patient showed slow improvement. The usual biochemical tests were carried out. The serum bilirubin level was normal, but the cephalin flocculation test produced a strongly positive result; the albumin-globulin ratio was inverted (0·35), hippuric acid excretion was low (0·7 gramme) and the prothrombin index was normal (86%). Aspiration biopsy in the seventh month of illness revealed gross disturbance in liver architecture. The liver cells were in clusters surrounded by fibrous tissue and inflammatory cells. Some pigment was present. The portal tracts contained great excess of fibrous tissue intermingled with inflammatory cells, mostly fibroblasts, lymphocytes and a few polymorphonuclear cells. There was some proliferation of bile ducts.

The patient was moderately well until three months later, when he developed an acute mastoid infection requiring operation. During this illness the jaundice increased and convalescence was prolonged. Chemical tests made after the operation revealed an increased serum bilirubin content (27 units), impaired hippuric acid excretion (1·5 grammes), a strongly positive response to the cephalin flocculation test and a high serum globulin level (6·7) with an inverted albumin-globulin ratio (0·45). The alkaline phosphatase level was only slightly elevated (26 units).

Comment.—This patient probably suffered from an attack of acute infectious hepatitis seven months before his admission to hospital. Subsequently he remained in chronic ill health, his liver and spleen remained enlarged and he often noticed slight jaundice. On his admission to hospital, biochemical tests and biopsy revealed the classical pattern of chronic active hepatitis. He relapsed three months later during an acute mastoid infection requiring operation.

SUMMARY.

1. Thirty-two cases of acute and chronic hepatitis have been studied by clinical observation, biochemical tests and biopsy of the liver. Autopsy examination has been made in three fatal cases.

2. It is considered that in most of the cases the hepatitis was caused by a virus infection. In one case dietetic deficiency existed and probably influenced the course of the disease.

3. No endeavour was made to isolate the virus or carry out specific serological tests, as other workers have failed to discover satisfactory methods apart from transmission experiments with human volunteers.

4. The history, symptoms and signs in the acute group (20 cases) were typical of the classical form of acute infectious hepatitis and consisted of fever, anorexia, upper abdominal discomfort, enlargement of the liver and often of the spleen, jaundice, dark urine and pale stools. The symptoms and signs usually resolved in four to eight weeks. One severe case ended fatally. No mild acute cases unassociated with jaundice, as described by Paul,[8] were discovered.

5. In the chronic group (12 cases) the condition had a variable onset. In some it began with a classical acute attack and failure to recover completely; other patients appeared to recover but later relapsed. In a third group there was no history of an acute attack, and it is presumed that the original infection was not detected because of the lack of symptoms and signs; yet it initiated a progressive chronic lesion. The patients in this chronic group drifted on for months or years with chronic weakness, lack of appetite and discomfort in the liver area. Jaundice was slight and sometimes absent. The liver was usually enlarged, tender and firm. Sometimes the spleen was palpable. Relapses resembling acute hepatitis occurred from time to time. A general trend of improvement was sometimes seen even after the patients had been ill for a year or more. Meanwhile they were vulnerable to infection, to chemical toxins, to surgical procedures, to trauma, to pregnancy, to prolonged mental and physical fatigue and to dietetic deficiency.

6. The biochemical changes in the acute group usually consisted of raised serum bilirubin level, increased urobilin output in the urine, pale stools later becoming dark in colour, a positive response to the cephalin flocculation test, reduced hippuric acid excretion, slight to moderate increase in the alkaline phosphatase level and a normal blood urea content. The prothrombin index was low and sometimes failed to rise when vitamin *K* was given parenterally. The cephalin flocculation test was the most informative single test in the differential diagnosis between acute infectious hepatitis and obstructive jaundice from stone or carcinoma. However, atypical results were occasionally encountered.

7. The biochemical tests were a valuable aid in the diagnosis of the chronic group. The changes were often similar to those seen in the acute group, except that the serum bilirubin level was only slightly elevated, the stools were of normal colour, and there was a reversal in the albumin-globulin ratio, due mainly to a rise in the globulin level. The most informative tests with regard to diagnosis and prognosis in the chronic cases were the cephalin flocculation test, the serum bilirubin test and estimation of the albumin-globulin ratio. The results of the tests were not always typical, especially during a quiescent period. Serial tests made at two-monthly intervals were a help in the prognosis.

8. Aspiration biopsy studies were of assistance in the making of a diagnosis in cases in which the question of operation for stone in the common bile duct or for carcinoma of the head of the pancreas was raised, especially when the results of the biochemical tests were inconclusive. They also gave some indication of prognosis. Nineteen examinations were made on seventeen subjects, no serious complications being caused. In the acute cases there was diffuse infiltration of the portal tracts and liver cell columns with inflammatory cells, together with signs of damage to the liver cells. Early fibrotic changes were also present. In the chronic cases varying degrees of degeneration and hyperplasia of the liver cells were seen, together with diffuse fibrosis and cellular infiltration, especially in the region of the portal tracts.

9. Treatment of the acute condition or of a relapse in the chronic condition consists of rest in bed till the acute phase is over, and then probably increasing exercise. In the case of severe relapse with drowsiness, the intravenous infusion of glucose and saline solution and of casein hydrolysate or serum appears to be of benefit; but the prognosis is grave. The patients with the chronic condition in remission were treated with a diet rich in protein and in methionine. Exposure to infection should be avoided, but if it occurs it must be regarded with concern. The chronically ill patients may begin to show improvement after months or even after a year or two of chronic ill health with relapses. Neither the patient nor his physician should despair.

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THE CONTROL OF SEX AND REPRODUCTIVE FUNCTIONS.[1]

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I BELIEVE I would have little difficulty in convincing you that sex and the products of the reproductive endocrines affect the functioning of higher centres of the nervous system. It is much more difficult to convince people that the central nervous system plays any role in the regulation of sex and reproductive phenomena. This latter is the task which has been set, however, and I will endeavour to do the best I can with it.

In order to place in their proper perspective the few influences which the nervous structures do have, I will describe in detail some of the neuro-humoral bases of (i) sexual and reproductive behaviour, (ii) sexual cycles, (iii) ovulation, (iv) parturition and (v) lactation.

Sexual and Reproductive Behaviour.

Behaviour requires function of the nervous system. The different levels of integration within the central nervous

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system operate in the production of various components of this sexual and reproductive behaviour. There is evidence of endocrine activity associated with some of these reactions; but first I will deal with the control of somatic and visceral muscle responses.

The psychiatrists and psychologists have so taken over and dominated this project of analysing sex and reproductive reactions that a physiologist, at least this one, feels somewhat hesitant about speaking. Anything I can say will sound rather anæmic in comparison with the colourful cultivated images painted by the sister sciences.

The reflex patterns of reactions of genitalia and limbs associated in mating are evokable in spinal animals and in men. The types of stimuli which elicit these reflexes are not very specific—the reaction often forms part of a mass response. In chronic bulbo-spinal preparations the reflex pattern is more complete, in that forelimb responses enter. The basic pattern of somatic and visceral responses is stamped upon the spinal cord.[1][2]

The autonomic system is responsible for the peripheral vascular components of the reaction. The sympathetic division in this instance cooperates with the sacral parasympathetic outflow in producing engorgement of the erectile tissue, the sympathetic nerves alone being capable of promoting a low-grade response in the absence of the lower two lumbar and the sacral segments of the cord which give rise to the parasympathetic outflow. As you know, sympathectomy in the female does not interfere with reproduction; but it causes sterility in the male. Removal of the abdominal chains or severance of the rami which contain fibres bound for the sacral region prevents ejaculation and the discharge of sperm.

The activity of these lower spinal reflex centres is controlled from higher levels of integration. Furthermore, ideas concerning sex and reproduction do not depend upon maintenance of neural contact with these lower centres and the reproductive organs, because animals with hind parts paralysed by severance of the cord or even by removal of the lumbo-sacral segments and the sympathetic chains will still show interest and signs of sexual excitement in the proper situations, especially if, to use a term coined by Steinach, "erotization" of the nervous system has been produced by hormones from the gonads.[1][2][3]

Nervous mechanisms lying within the diencephalon effectively integrate the female mating responses. In guinea-pigs and cats mating in normal males will occur when practically all but the caudal hypothalamus or the mesencephalic region has been removed. The female is deficient only in her "approach tactics". The maternal reactions are also absent, although parturition may occur with some degree of normality.

There appear to be within the hypothalamus and upper brain stem (i) centres which are capable of modifying the level of sex endocrine activity presumably by modifying the hormone output of the hypophysis, and (ii) centres which are involved in receiving impulses and organizing patterns of responses essential to reproductive reactions of males and females. Electrical stimulation of the hypothalamus heightens the hormone output and elicits characteristic sexual somatic reactions.[2][3][6] Other excitatory influences exerted there do the same. For example, sexual disturbances are commonly associated with lesions of the hypothalamus. Some tumours and lesions apparently produce overactivity and development, while others result in sexual dystrophy

Cases of precocious puberty are rare. None have been produced experimentally. *Pubertas præcox* most commonly occurs in association with tumours of the adrenal cortex or gonads; but some examples have resulted from *encephalitis lethargica*, from measles, meningitis *et cetera*, while others have been caused apparently by pineal or hypothalamic tumours The pineal tumours conceivably directly and indirectly exert pressure stimulation, and it has been suggested that other effective tumours exert a stimulating effect. Two things are clear: (i) in practically all cases reported by Riddoch, Dott and others[13] the tumours impinge upon the mammillary region, and (ii) there is a hyperactivity of gonadotropic hormone secreting mechanisms as indicated by urine analysis. Irritative manipulations of the hypothalamus are commonly followed by signs of sexual excitement and increased gonadotropin output.[3][12]

Lesions, destructive tumours and ablations of portions of the hypothalamus produce genital dystrophy, lowered sexual tone and a lower level of gonadogen output. Such lesions are generally located more rostrally in the anterior part of the hypothalamus. Experimental production of genital dystrophy and cessation of cycles and sexual activity have been accomplished by the production of large lesions in the anterior part of the hypothalamus just caudal to the optic chiasm. In this case, though there is much variation, it seems that there has been an interruption of a hypothalamic driving mechanism which promotes activity in the hypophysis. All one can say is that anterior lesions generally produce dystrophy, while in precocious puberty tumours are commonly found in a caudal mammillary locus.[2][3][7][13]

It has been shown, however, that the genital dystrophy associated with tumours of the hypothalamus is frequently due to injury of the hypophysis. Furthermore, much of the dystrophy associated with obesity is secondary to excess fat deposition. In many cases of delayed puberty in fat children weight reduction will bring about normal development. Sterility may likewise be produced by impingement of fat masses upon the reproductive organs and channels. Obesity-producing lesions may secondarily cause reproductive abnormality. There are a few cases in the literature of clinical and experimental laboratories, however, which seem to indicate that sexual dystrophy and hypogonadism have originated from a lesion which impairs the normal activity of the hypophysis without directly injuring it. Here we have reached an impasse—is there an essential humoral or neural link between certain mammillary or other hypothalamic nuclei and the anterior lobe of the hypophysis? Results are still contradictory.[3][13]

What is the Role of the Cerebral Cortex?

A comparison of the effects of forebrain injury on the reproductive life of fishes, amphibia, reptiles, birds and mammals indicates that with cephalization certain changes occur. (i) The variety of external stimuli capable of evoking sexual responses tends to increase. (ii) The overt pattern of expression tends to become more variable. (iii) The direct importance of the gonadal hormones to sexual behaviour tends to decrease. It is certainly true in man that conditioned responses are determinant—not hormones. In lower forms androgens for males and œstrogens for females are essential to the "sensitizing" of the reaction pathways. Mating will not occur in their absence. In man, however, they are not essential.[3]

The male's performance is more dependent on the cerebral cortex. He is dependent upon distant reception, while the female responds primarily to contact reception. Removal of temporal cortex may "uninhibit or release" sexual responses of males and females; but removal of between 20% and 60% of the total cerebral cortex inactivates males. All other activities are similarly reduced—vigilance, attention, somatic activity *et cetera*. The male plays the initiating role, and with loss of cortex he loses his direction and drive. It is my feeling that it is the number of sensory and motor defects created which is the important thing, not the mass of cortex. Large removals impinge upon more sensory and motor areas and are bound to reduce the factors of safety and the number of possible alternative pathways of perception.[2]

The psychologists deserve the credit for obtaining experimental substantiation of a thing which we should all guess would occur: that if a male and female rat are placed in opposite ends of a box with an electric grid in between, the male is more likely to take a shock and join the female if she shows signs of wanting him with her. A second technique of measuring and comparing the strengths of basic drives indicates that sex may not be so all-important after all. A male rat which has been starved for twenty-four hours is placed in a box and confronted with two doors. He perceives that by passing through one door he will be with a female rat in œstrus, but by entering the second door he will get food. Male rats take the food 80% of

the time as first choice, and if starved longer they take food 100% of the time.[16]

The cerebral cortex mediates the finer elements of this type of behaviour, and it is essential to maternal reactions such as care for the young, nest building *et cetera*. Its control is exerted upon more primitive levels of response.

Reproductive Cycles.

Not all mammals and birds have the same type of reproductive cycles. The various species can be subdivided into groups with respect to these variations.[3][14] (i) The majority of mammals and birds have a seasonal œstrus cycle. (ii) A second group are polyœstrous, in that this cycle proceeds without influence of season. Cycles are short and frequent. Some of the normally wild species (mink) become polyœstrous in captivity when kept under uniform environmental conditions. (iii) The third type of cycle is the primate and human menstrual cycle.

This classification is rather general. Volumes have been written concerning the various cycles and their peculiar time sequences. One does wonder how the ovary keeps the time and can perform so regularly.

Seasonal Œstrus Cycles.

Marshall[14] makes the following statement:

> In view of the general correlation between the seasonal and the sexual cycles it must be assumed that these stand in the relation of cause to effect, unless one believes in pre-established harmony, and nowadays it is not fashionable to believe in pre-established harmonies.

Aristotle realized this relationship between environmental change and sexual periodicity, because he said: "Where the weather is warm and fine and food is abundant sheep may have young twice a year." I do not know where that place is, but I do know that animals can adapt their cycles to the seasons. Red deer and the sheep of Europe rut in the autumn of the northern hemisphere, when daylight is diminishing. When transported to the southern hemisphere they likewise rut in the autumn, but in the southern hemisphere's autumn. About sixty years ago the first red deer were sent to Otago from England, and shortly thereafter some wapiti were presented to you by Theodore Roosevelt, which had come from our western ranges. Almost immediately the change-over was made by these deer. They did not have young the first season, but from then on rut began on about March 20 instead of in November. Deer have been imported to New Zealand from various parts of Scotland, England and the Continent. No matter where they come from, they all begin roaring about the third week in March.

To make a long story short, it has been found that the intensity and the daily periods of light are factors promoting sexual activity. It is the visible part of the spectrum which is effective. As the days lengthen in the spring time, or as the hours of exposure to light are increased experimentally under controlled conditions, the ovaries of spring breeding birds and mammals begin to develop. If the animals are hooded or if their optic nerves are cut, light is ineffective and periodicity is abolished. There are species variations, but it is clear that the eyes receive stimuli which are transmitted through the nervous pathways of the hypothalamus to the anterior lobe of the pituitary gland, though no one has fully determined the pathway which they follow. It is well known that light affects secretion of melanophore hormones of the pituitary by way of visual pathways—there are known pathways in some forms.

Again I should mention species differences, because some animals seem to respond to the decrease in light of the autumn (sheep and deer). The abundance of favourable foods may play some part here, because many seed-eating birds nest rather late towards the autumn. Some birds do not conform when transported to new climates. Birds from North Australia (the hooded and the brown parrakeet are examples) are markedly more inclined to stick obstinately to their own breeding season (October) even when transported to the northern hemisphere. Some birds try to keep both seasons and moult and breed at their old season and also in accord with the new (grass parrakeets and Bourke's parrakeet). South Australian and Central Australian parrakeets adapt themselves very promptly, while other species of birds and mammals adapt themselves but require a year or two of exposure.[3][14]

Here in these diverse species we have a little-studied wealth of examples of the influence of external stimuli on reproductive function. These exteroceptive stimuli must pass through the central nervous system to elicit the activity of the hypophysis. There is no real evidence of the effect of light on sexual periodicity of mankind—if one disregards poetical reference to lunar rays and some other rather lurid stories about the Eskimos—but that is all right, because man possesses another type of cycle (Table I).

TABLE I.
Cycles.

Mammals.	Birds.
1. *Seasonal.* (*a*) Modifiable. Most species, demonstrated in deer, sheep, mink, ground squirrel, mice *et cetera*. (*b*) Not modifiable. Few species, demonstrated in spermaphiles.	1. *Seasonal.* (*a*) Modifiable. Most species, demonstrated in starlings, ostrich, ducks, South Australian parrakeets *et cetera*. (*b*) Not modifiable. Few species, demonstrated in weaver finch, paradise whydahs, north Australian parrakeets *et cetera*.
2. *Non-Seasonal.* (*a*) Irregular in foxes, otter, horse and some other captive forms. (*b*) Polyœstrous cycles — rats, white mice, guinea-pigs *et cetera*. (*c*) Menstrual cycles—Old World monkeys, primates, man.	2. *Non-Seasonal.* (*a*) Irregular in lovebirds, lorikeets and some other tropical birds. (*b*) Polyœstrous—ring dove, pigeon, fowl *et cetera*.

The Œstrous Cycle and Menstrual Cycle.

The œstrous cycle and the menstrual cycle are independent of season and are relatively independent of external influences for their initiation. Practically all the evidence available indicates that they are completely humorally mediated endocrine cycles. However, neurally mediated influences do break in upon the normal cyclical procession of events.

In mice and rats and other polyœstrous animals with a very short four to five day cycle the *corpus luteum* has such a short life that it does not fully sensitize the uterus to receive and implant a fertilized ovum. Thus these species have developed a peculiar response called "pseudopregnancy". On mating or on sterile coitus or on electrical or mechanical stimulation of the cervix a reaction takes place which prevents degeneration of the *corpus luteum* for eight to twelve days. The uterus is sensitized, the fertilized egg is implanted and a placenta is formed under the influence of the *corpus luteum* hormone. This reaction suggests a reflex or emotional stimulation of the hypophysis by way of the hypothalamus, because the sympathetic nerves are not involved and other peripheral chemical influences have not been discovered. Just how the hypophysis is stimulated and just how the *corpus luteum* is prevented from degenerating is still not known.[3]

Emotional disturbances affect the menstrual cycle, and surgical procedures such as section of the splanchnic nerves, section of the ventral roots of the lower cord segments or hemisection of the cord are followed by menstrual-like bleeding. This is probably due to temporary impairment of ovarian function due to vascular or other changes which result in a type of œstrogen or œstrogen-progesterone deprivation menstruation.

The rhythmic œstrous and menstrual cycles are the result of humoral interrelationships between the ovaries and the pituitary gland. Seasonal œstrus has a similar sequence of events and a similar explanation. This rather complicated scheme of things is explained by the fact that follicle-stimulating hormone is responsible for terminal follicular growth. Follicle-stimulating hormone and a small amount of luteinizing hormone stimulate

further follicular maturation and œstrogen production, which in turn increases the amount of luteinizing hormone produced and reduces follicle-stimulating hormone production. Large amounts of luteinizing hormone and probably small amounts of follicle-stimulating hormone induce ovulation. The *corpus luteum* develops under the influence of luteinizing hormone and becomes functionally active in the presence of lactogenic hormone (luteotropin is now the lactogenic factor).[10]

Figure I compares the œstrus and menstrual cycles and merely indicates that catamenia is a terminal phenomenon associated with regression of the endometrium. If one should take ovulation as the starting point of the cycles, the cause and sequences of ovarian changes would be the same.[5][10]

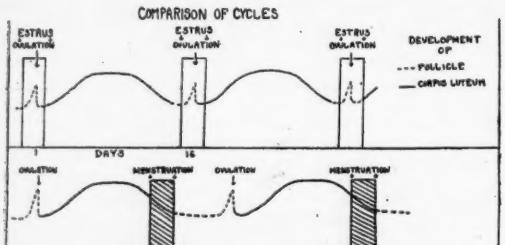

FIGURE I.

A diagrammatic comparison of the œstrous and menstrual cycles.

Central nervous system lesions do affect these cycles and abolish or prolong them; but the variation in position of effective injuries has been such that analysis of the mechanism of action is not yet complete.

Ovulation.

Animals with œstrous cycles ensure fertilization of ova by mating only at the time of ovulation. Primates with a menstrual cycle ovulate spontaneously, but have no heightened desire at the time of ovulation—they just mate all the time. There is a final group of animals which insure impregnation by ovulating only on mating. The cat, the rabbit, the ferret, the mink and the short-tailed shrew and the pigeon belong to this last type.

Spontaneous ovulation is due to synergistic functioning of certain glands. The ovaries of man at birth contain several thousand ova. Through some process still unknown, some of these ova are constantly beginning to develop, while others remain in a primordial state. Most of these ova do not attain maturity, and only 400 or so follicles reach the stage of ovulation and discharge a mature ovum. The remainder develop within follicles which fail to mature and rupture.[5]

For the final steps of development to occur the follicle-stimulating hormone of the hypophysis is essential. I have already described the way in which follicle-stimulating hormone is supplemented by luteinizing hormone in maturing the follicle, and how the œstrin-stimulated increase in output of luteinizing hormone *plus* a little follicle-stimulating hormone causes ovulation. The egg breaks from the follicle either because the increased pressure of follicular fluid ruptures the wall or because the wall becomes weak from enzyme action upon it or from pressure ischæmia. Spontaneous ovulation requires no neural timing of the action of the hypophysis.

Induced ovulation is due to a specific excitation of the hypophysis by way of a hypothalamico-hypophyseal connexion. In the rabbit, for example, coitus causes the anterior lobe of the hypophysis to liberate an ovulation-producing hormone which is probably a mixture of follicle-stimulating hormone and luteinizing hormone. The rabbit's ovary matures a group of follicles when she first comes into heat; but these follicles do not rupture, nor does the ovum pass through the final maturation division. The initially mature follicles regress and a new crop arise approximately every seven to ten days; but there are always sufficient mature follicles and ova present in the female's ovaries and sufficient œstrogenic hormone is secreted to maintain interest and the possibility of ovulating until the female meets a congenial male rabbit.[3][6]

It is not the act of mating or the vaginal or cervical stimulation but the peak excitement engendered thereby which causes ovulation. Denervation of the caudal regions of the body does not prevent ovulation. It is not the semen or the clasp reaction or any specific sensory stimulation which causes ovulation. The only thing essential is that the animal reach a sufficiently intense peak of excitement. Convulsive drugs, such as picrotoxin and "Metrazol" and copper salts, when injected produce ovulation. Electrical stimulation of the spinal cord or hypothalamus also elicits the reaction. Section of the sympathetic nerves to the hypophysis, or removal of various other endocrines acutely, does not abolish the reaction; but severance of the hypophyseal stalk does prevent ovulation, even though assays of the gland show that it contains the normal content of ovulation-inducing materials.

There are still some holes in the evidence; but until a better hypothesis is put forward it is safe to conclude that in those species in which ovulation must be induced, it is the attainment of a general level of excitement which causes impulses from the hypothalamus to activate liberation of ovulation-producing hormones from the anterior lobe of the hypophysis. Mating generally succeeds in producing a sufficiently intense excitation.[4]

The seventeen-year locust has the longest and the fowl has the shortest ovulation cycle of all animals. A good fowl lays approximately one egg a day under proper conditions. A hen requires no less than twenty-five to twenty-eight hours to produce an egg, but she will not lay in the dark. If the evening hours overtake her before her egg is laid (a fowl rarely lays after 4 o'clock), ovulation is inhibited until the next day and the farmer loses an egg unless he artificially lights his hen house.

Ovulation in birds is inhibited by other phenomena. After a bird lays her normal number of eggs in a nest, she stops laying and broods. If an egg is taken away each day, as is done in the case of the fowl, a robin or other wild bird will continue to lay until twelve or twenty eggs are produced instead of the normal three or four. Why does feeling or counting four eggs stop ovulation?

Finally, we have the pigeon which will not ovulate if she lives alone. She probably prefers a male mate, of course, but another pigeon in a nearby cage will do, or another bird with her which looks a little like a pigeon will do, and I am told that she will also be reasonably content and continue to ovulate in the absence of all company if she has a mirror in which she can see herself.

Thus we have this gamut of exciting experiences which are essential to ovulation in some forms. There is evidently a hypothalamic mechanism involved in the excitation of the necessary hypophyseal activity, although the pathways and nature of the activating force are not fully known.[9]

Parturition.

Dale in 1909 first described the oxytocic action of posterior pituitary extracts. The use of oxytocic extracts has moved in and out of accepted obstetrical practices and it has been studied much; but its physiological significance is still undecided, though its presence certainly suggests some possible function during parturition. Stimulation of the pituitary does release a substance which will cause the uterus to contract.[3] Oxytocic material is liberated from the pituitary towards the end of pregnancy; but this evidence is somewhat invalidated by claims that the posterior lobe is not necessary to parturition or is at least not indispensable.[10] Ablation of the posterior lobe of the hypophysis or interruption of the hypothalamico-hypophyseal connexions does tend to be followed by abnormal labour.[7][8][17] In animals with experimentally produced *diabetes insipidus* labour is frequently unsuccessful; however, it is quite normal in some individuals, both human and subhuman, who have *diabetes insipidus*. Even if we

assume that the posterior lobe does discharge its oxytocic hormone to aid labour, we still do not know the nature of the possible stimulus.

The commonly accepted contributory causes of labour and parturition are the degeneration of the *corpus luteum* and the release of the uterus from its depressing or quieting influence; but this is not a completely adequate explanation either, because the ovaries can be removed from some forms without causing abortions—the placenta takes over; placental degeneration must then cause labour, but why does the placenta degenerate at a specific time?

When one of the world's leading students of reproductive phenomena states that "the physiologist who looks for one specific cause of the onset of labour is up against the same kind of problem as the economist who tries to find one single cause for a stock market crash or to pin down a nationwide problem of unemployment to one specific factor", I think I can be forgiven for admitting that though here again we have suggestions that neurohormonal reactions may be involved, little evidence is available really to substantiate the claims.

Extrinsic nerves are not essential to uterine action in parturition, but there are phenomena which suggest that nerves do act in controlling uterine reactions. (i) Emotional disturbances will bring on premature parturition and (ii) suckling is supposed to provide a stimulus which increases contraction of the uterus *post partum*.[10]

Lactation.

Lactation is a phenomenon associated with reproduction which presents some problems related to our theme—the neuro-endocrine control of reproduction. Lactation begins following parturition; why does it begin then? What mechanisms operate in its prolongation and inhibition? The phenomenon suggests a sudden beginning and ending of an endocrine-mediated function.[13]

Here again we are confronted by a host of species differences which interest the biologist and physiologist but tend to bore the clinician, until it can be shown that these mechanisms which are so clearly seen in lower forms because of these species' specialization may also be playing at least minor roles in the human being's function.

In most species a synergistic action of hormones is required for the development or proliferation of mammary gland structures and the beginning of lactation. The œstrogens exert the initial stimulating effect, arousing the major ducts from their resting state, begin a proliferation of the duct system and sensitize the structures to the action of the *corpus luteum* hormone. Œstrogens cause duct growth.

Progesterone provides the stimulus for the development of the lobule-alveolar system, and under its influence full development of cells and ducts is attained, but milk formation does not occur. Progesterone will not operate upon glands which have not been sensitized by œstrogens. Nor will the lactation-producing hormone which comes from the acidophile cells of the anterior lobe of the hypophysis produce milk secretion in a gland which has not previously been acted upon by the œstrogens and progesterone. This lactogenic hormone or prolactin is secreted by the hypophysis following parturition.

Evidence has been presented that adrenal, thyreoid and hypophyseal hormones (other than lactogenic hormone) play a part synergistically. The thyreoid hormone is necessary for formation and existence of eosinophile cells in the anterior lobe of the pituitary. In its absence the reproductive hormones are lacking. Placental hormones are also involved as well as the state of nutrition. To say this is merely to restate the thing which you already know but which many of us forget: the body functions as a whole, and any small neural, endocrine or nutritional defect has far-reaching consequences.

During each cycle (menstrual or œstrous) the mammary glands are exposed to œstrogens from the follicles and after ovulation to progesterone. Some mammary gland development does occur, as you know; but during pregnancy both œstrogen and progesterone action are much more prolonged and a greater development occurs.

There are species differences which contradict what I have just said to certain degrees. One wonders how different they really are, because many experiments performed to judge the effect of œstrogens alone were done by injecting the material into normal animals—the œstrogenic material may have stimulated release of other hormones from ovaries and hypophysis. Some of the species differences stated are these: (i) Lactation has been artificially induced in cattle by administration of synthetic œstrogens (diethylstilbœstrol). This is evidently more easily done in heifers than in adult cows which have experienced normal lactation. In most species stilbœstrol will produce marked mammary development but no lactation. (ii) The guinea-pig requires only œstrogens for full mammary gland development. Œstrogens *plus* lactogenic hormone produce lactation. (iii) In the primates progesterone facilitates development of ducts and alveoli, but it is not absolutely necessary.

The hypophysis is essential to the development of the mammary glands as well as to lactation. The placenta may sustain development if hypophysectomy is performed during pregnancy; but lactation cannot occur without lactogenic hormone of the anterior lobe. Species vary, but in many cases œstrogen *plus* progesterone will not cause mammary development in hypophysectomized animals unless lactogenic hormone is also injected.

Lactogenic hormone usually fails to increase lactation in poorly lactating individuals, because usually the hypoactivity is not due to hormone lack. However, the hormone will prolong the period of lactation and prevent involution.[13]

Pigeons do not have mammary glands; but this lactogenic hormone is involved in the production of a kind of milky secretion from crop glands which is fed to their nestlings. Toads, frogs and salamanders likewise have no mammary glands, but in these species the jelly envelope secreted in the oviduct to serve as a protective covering of the eggs is secreted under the influence of a lactogenic factor from the hypophysis—pigeon or mammalian gland extracts stimulate the oviduct (Corner[9]).

There are two prerequisites for lactation: (*a*) a well-developed mammary gland and (*b*) high lactogenic hormone content of the anterior lobe of the hypophysis.[13] These two requirements are generally satisfied early in pregnancy; but lactation usually does not begin until after parturition. Why does it begin then?

There are two points at which milk secretion may be under the influence of neurally stimulated hormone production.

There is evidence that such a mechanism may operate to start lactation at parturition. The commonly heard theories of the origin of lactation are as follows. (i) Milk flow begins when uterine distension is released by discharge of the fœtus. This has largely been abandoned, because prevention of uterine collapse by insertion of paraffin masses does not inhibit lactation and nursing of young. (ii) Lactation begins with loss of the placenta, the œstrogenic materials produced by the placenta holding the output of lactogenic hormone from the pituitary in abeyance until the placenta is cast. It is true that œstrogens as well as testosterone have been used to check lactation. They will not check it if given simultaneously with lactogenic hormone, so they must act on the hypophysis. Unfortunately this likewise is not a completely satisfactory theory, because it has been reported that full lactation can be established before parturition by "milking" the already well-developed glands (Peterson[15]). Furthermore, we have the strange phenomenon that œstrogens alone will enable lactation to start in certain species (cows). (iii) Finally we have the suggestion that stimulation of the glands by suckling or milking or by irritating substances will reflexly initiate lactation through release of and stimulation of increased lactogenic hormone production by the anterior lobe of the hypophysis. If the glands are not stimulated and milk is not removed, the pressure of the milk in the ducts and alveoli eventually checks the activity of the lactogenic cells, and the production of lactogenic hormone also subsides after reaching a certain concentration in the hypophysis.[13] (*a*) Milking increases

the output of milk and the level of production of lactogenic hormone. (*b*) When milking does not occur, the mammary glands of goats and cattle regress within thirty days and no milk is formed. If one-half of the udder is emptied, regression in the unmilked half is enormously retarded. (*c*) Ingelbrecht[11] claimed that rats with spinal transection between the last thoracic and first lumbar segments showed involution of all mammary glands if only those nipples below the lesion were sucked. If those above the lesion were sucked, all glands retained activity. It was thought that afferent nerves were stimulated which reflexly stimulated a lactogenic hormone output. (*d*) Periodic electrical or chemical stimulation retards gland regression and prolongs ability of the glands to produce milk even though milking does not occur. (*e*) Suckling increases the amount of lactogenic hormone in the hypophysis (Reece and Turner[13]). (*f*) When ducts are tied off or cut and no milk can leave the gland, suckling still prevents involution despite the high intraalveolar pressure due to trapped secretions.[6] (*g*) More frequent milking yields more milk. This may be due to release of the pressure block to milk flow or to a stronger and more frequent stimulation. This "suckling" or "lactation reflex" is thought to be mediated by the hypothalamic-hypophyseal connexions; but proof of this is still inadequate to my way of thinking, because the required control experiments have not been done (stalk transection *et cetera*).

2. The second phenomenon which may involve a neural mechanism of lactation is the discharge of milk from the ducts or the "let down" reaction. You will find in the literature some arguments about this "let down" reaction in milk cows. It is a question of whether stimulation of the teats elicits an outpouring of oxytocic hormone from the pituitary which contracts the alveoli and the ducts and makes milking a reasonably easy procedure. Well, my Irish grandfather and an old Jersey cow named Bessie used to have that argument out every morning and evening; but I do not remember that they used those words and that vocabulary.

Lactating women become conditioned to certain stimuli, and a very strong reaction of the mammary glands occurs which favours profuse lactation. According to this theory the "let down" or discharge of milk from the mammary gland is favoured by a contraction of alveoli and the duct system under the influence of the oxytocic hormone of the posterior lobe of the hypophysis. Many believe that nervous reflexes of suckling or stimulus origin evoke their effect through this reaction rather than by affecting milk secretion. (*a*) Posterior hypophyseal extracts do have milk-expressing properties. (*b*) Within forty-five seconds after the application of a stimulus to the teats of a cow, the "let down" reaction occurs; the originators of this observation calculated that was just time for oxytocic hormone to be liberated and reach the gland. Furthermore, the blood from a cow stimulated to "let down" will cause "let down" in perfused excised glands; but blood from a cow not so stimulated will not produce "let down". This is remarkable if true, and must be due to some reflex excitement of the posterior lobe of the hypophysis mediated by the hypothalamus. Excitement tends to prevent the response to milking stimulus, and the ducts and alveoli tend to retain the milk. Failure of lactation in neurotic women is probably due to some such phenomenon of inhibition. The less complete evacuation of the gland leads to involution.

This picture of an oxytocic factor in lactation processes is not completely clear. According to the English school (O'Connor) excitement produces an increased discharge of antidiuretic hormone from the posterior lobe of the hypophysis, and unless we assume that the oxytocic release behaves independently, excitement should cause the uterus to contract and the mammary duct systems to "let down" milk. Problems remain here. Smith and Haussay have claimed that lactation occurs normally in dogs and rats after removal of the posterior lobe of the hypophysis; but more modern studies of the extent and distribution of the secretory elements of the *pars neuralis* would suggest that removals were not complete. There are cases in the literature of human individuals with *diabetes insipidus* who successfully gave birth to and reared a child, but nursing may have been done with a battle. Although the statement is generally made in textbooks that "unquestionably the nervous system is involved in lactation", I personally would like to see some more carefully done and more completely controlled experiments before accepting the conclusion without reservation. If these hypophyseal activities of either the anterior or the posterior lobe are nervously controlled, the nerves responsible reach the gland by way of the hypothalamico-hypophyseal system. Severance of the sympathetic supply is without effect.[3][4]

The rate of milk secretion diminishes as the milk accumulates in the alveoli. The concentrations of a few substances in milk and blood are the same (urea, creatinine *et cetera*); but normally in terms of molar concentrations the concentrations in milk as compared to blood are as follows: fat, 20:1; sugar, 40:1; potassium, 7:1; calcium, 14:1; while blood contains twice as much protein, four times as much chlorine and eight times as much sodium as does milk. These differences in concentrations are due to secretory activity of the gland tissues. Some of the fat of milk may be produced directly by the gland from carbohydrate—its respiratory quotient is above 1·0. The cells of the alveolar wall are small cuboidal cells which gradually become filled with secretory material and elongated at the inner end. This part of the cell then breaks off, thus releasing the materials which comprise the milk. These cells then resume their original squat form and the cycle begins again. Five or more of these cycles occur within twenty-four hours. Milk is formed at a uniform rate day and night; but if milk is not removed from the gland secretion eventually ceases as external pressure builds up beyond a certain point. The materials then begin to come into equilibrium with the blood. Eventually all the milk is resorbed and gland involution occurs until the next reproductive period begins.[12]

Conclusion.

I have thus placed before you a rather bewildering array of observations, theories and facts. It must be obvious to you that much more work is required before we can choose between various diverse suggestions and find out what are the basic mechanisms underlying these reactions.

The nervous system participates in a few sex and reproductive functions. Its role varies enormously in various species, but in all forms some neural activity is involved. The somatic motor functions are integrated by a hierarchy of centres, and certain endocrine phenomena are influenced to some degree by hypothalamic mechanisms. I have endeavoured to outline the present state of our knowledge concerning this field.

You may be more strongly convinced than ever that the endocrines exert a more powerful influence upon the central nervous system than that exerted by the higher neural centres on the sex glands. But I suggest that even if you do feel that way about it, just as many mysteries remain. How do these chemical influences modify the excitatory and inhibitory complexes of nervous system activity which control behaviour? We have not even theories of how they operate despite the fact that their action is profound.

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Reports of Cases.

A CASE OF LEIOMYOMA OF THE TRANSVERSE COLON CAUSING OBSTRUCTION IN A CHILD.

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LEIOMYOMATA, other than uterine myomata, are relatively rare, and of those occurring in the intestinal tract, tumours of the colon are by far the rarest. J. E. Morison,(1) in a review of 13,139 cases of gastro-intestinal tumours over a period of ten years, could find only two leiomyomata, and both of these were in the small intestine. Ehrlich and Hunter,(2) in a survey of 813 cases of gastro-intestinal neoplasms in persons of military age, during the second world war, describe fourteen benign leiomyomata, and of these, one occurred in the large intestine. Thirty cases of leiomyomata of the gastro-intestinal tract are described by Golden and Stout,(3) but only two occurred in the colon. Of these 30 cases, in 21 the growths were classified as being malignant. The average age of occurrence was forty-seven years. Foster(4) describes a leiomyoma of the ascending colon causing clinical signs in a man, aged forty-one years.

No case of a leiomyoma causing signs and symptoms of obstruction in a child could be found in the literature available. Because of its rarity the following case is submitted.

Clinical Record.

B.W., a male child, aged five years, was admitted to the Perth Children's Hospital on May 31, 1947. During the preceding two years the child had had two attacks of vomiting, one such attack being accompanied by colicky abdominal pains. In March, 1947, the child experienced another attack of vomiting with abdominal pains. The vomitus was described as having been always of a yellowish colour. These vomiting attacks could not be attributed to any particular physical or mental factor. The child had never suffered from constipation, nor had there ever been blood or mucus in the stools. His appetite had always been poor, but he did not appear to have been losing weight recently. There was no relevant family history.

Two weeks prior to his admission to the Perth Children's Hospital, physical examination of the child by a country practitioner revealed a large, round tumour in the epigastric region of the abdomen. This finding, with the history of abdominal pains and vomiting, caused the presence of an intussusception to be suspected. Laparotomy was performed, and a mass, described as a tumour of the colon, was found in the mesocolon, attached to the posterior gastric wall. As carcinoma was now suspected, the abdomen was closed and the child was sent to Perth for further investigation.

Upon the child's admission to hospital, examination revealed him to be pale, with a normal temperature, and in a fair state of nutrition, though under-sized for his age. The tonsils were enlarged and chronically inflamed, and the right tympanic membrane was red. A vertical right paraumbilical crusted scar was visible on the anterior abdominal wall, and a firm non-mobile non-tender mass, about the size of a small orange, was palpated just below the epigastrium. The heart, chest and central nervous system appeared to be normal.

On June 4 microscopic examination of the urine showed it to be normal. A flat X-ray film of the abdomen on that day revealed an area of dulness behind and above the stomach. A Casoni test, a Mantoux test and a Wassermann test all produced negative results. The hæmoglobin value was 11·5 grammes *per centum*.

On June 7 the temperature rose to 103° F., and the child was found to have follicular tonsillitis and right *otitis media*. The administration of sulphamerazine for four days rapidly cured this.

On June 12 the abdominal scar looked clean, and the crusts had separated. Laparotomy was decided upon. To this date no further abdominal pains or vomiting had occurred, and the child's bowels had acted normally.

Under ethyl chloride and "open ether" anæsthesia the peritoneal cavity was opened by an upper left paramedian incision. Adhesions about the site of the previous laparotomy were divided, and an opening into the lesser peritoneal sac was made by incision of the gastro-colic omentum. A large, firm tumour was found in the transverse mesocolon, attached to and apparently arising from the transverse colon, and adherent to the postero-inferior aspect of the stomach. Attempts to separate the tumour from the gastric wall caused free hæmorrhage. No evidence of metastases could be seen, but because of the intimate adhesions to the gastric wall, it was decided to resect that portion of the stomach to which the tumour was adherent. The remaining edges were oversewn with a double layer of gut sutures.

A loop of transverse colon containing the tumour was then exteriorized, a spur was formed, and the peritoneum was sewn closely about the emerging limbs of the loop, which were then ligated with catgut, and about five inches of colon containing the tumour were then removed.

Macroscopic examination of the specimen revealed a hard, round mass, about four inches in its widest diameter, projecting into but not ulcerating through the transverse colon. It cut with a rubbery feeling, and presented a pinkish cut surface. The report on a microscopic examination of a section was as follows: "Fibromyoma. Mucosa normal. No suggestion of malignancy apparent."

Post-operative procedures included, *inter alia*, the intravenous transfusion of whole blood and serum, and continuous gastric suction. The ligatures on the emerging limbs of the colon were removed on June 15, and, after the colostomy had worked well for seven days, a crushing clamp was applied to the spur on June 22. This remained in place for a further eight days, when it was considered that sufficient of the spur had been crushed, and the clamp was removed.

Firm pressure upon the exteriorized colon sufficed until August 1, when, under ether anæsthesia, the bowel forming the colostomy was freed from the abdominal wall and returned to the abdominal cavity, and the opening was closed with gut sutures.

X-ray examination of the chest and abdomen on August 26 failed to reveal any pathological process, and the child was discharged from hospital in good health on August 28 with instructions to return to an out-patient clinic.

Discussion.

Whilst leiomyomata are considered generally to be benign tumours, it is rather significant that of the 30 cases presented by Golden and Stout,(3) in 21 the tumours were classified as being malignant. To quote these authors:

> One can never be entirely certain that any leiomyoma is necessarily benign, except small intra-mural types.

Any of the tumours, large enough to cause clinical symptoms, may kill by infiltrative growth, or, occasionally, by metastases.

Similarly, O. N. Smith,[5] in a review of 109 cases of leiomyomata of the small intestine, showed that 16% of these growths metastasized.

Points in favour of a good prognosis in the case discussed are: (i) absence of erosion into the colon or stomach; (ii) absence of metastases to regional lymph nodes; (iii) wide excision of the tumour; (iv) relative absence of mitotic figures and general metaplasia.

Summary.

A case is presented of a benign leiomyoma of the transverse colon in a child of five years causing signs and symptoms of intestinal obstruction. Successful surgical removal of the tumour is believed to have been achieved.

Acknowledgements.

My thanks are due to the Medical Superintendent of the Perth Children's Hospital, and to the honorary surgeon concerned, for permission to publish this report.

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Reviews.

RARE DISEASES.

"RARE DISEASES AND SOME DEBATABLE SUBJECTS", by Dr. F. Parkes Weber, of London, has appeared in a second edition only one year after its original publication.[1] This is indicative of the favourable reception it has deservedly met. It has been enlarged from 170 to 192 pages chiefly because of the interpolation of supplementary facts and theories of a "debatable" nature.

Dr. Parkes Weber has endeavoured to clarify the nomenclature of numerous syndrome-complexes by ingenious grouping, and in doing so he has displayed wide acquaintance with uncommon syndromes and masterly scholarship in associating them, no matter how loosely.

As an instance, attention may be drawn to his favourable reception of the term "palendromic rheumatism", introduced in 1944 by Hench and Rosenberg, who thus described a large series of cases of recurrent afebrile attacks of acute arthritis and periarthritis. Dr. Parkes Weber likes the vagueness and non-committal nature of each of these two words. He proposes that we should use them in a wider sense to include recurrent hydrarthrosis originally described by Schlesinger in 1899 and also some allergic conditions involving joints or their vicinity. He speculates on the possibility that some process resembling allergy may be operative as a common factor. He appends two case histories to illustrate even more complicated syndromes that may fit into the framework of palendromic rheumatism.

In another chapter he discusses the question of acute chronic allergic or allergy-like conditions and the bearing of the question on classification and therapy. He states that authorities no longer hold the view that epituberculosis may represent a chronic allergic response towards a tuberculous focus. He also raises many important questions concerning the role of allergy in acute rheumatism.

In the final chapter symptomatic sclerodermic conditions and sclerodermia are discussed briefly, but the condensed notes and comments are very informative and interesting.

[1] "Rare Diseases and Some Debatable Subjects", by F. Parkes Weber, M.D., F.R.C.P.; Second Edition; 1947. New York, Toronto and London: Staples Press, Limited. 8¼" × 5¼", pp. 192, with many illustrations.

The little book is packed with unusual facts and the commentary is likely to stimulate thought—philosophical and scientific. Among Dr. Parkes Weber's whimsical reflections we find that he approves of the increasing proportion in the community of elderly people consequent upon improvements in dietary and advances in medicine because more knowledge can be acquired in the extra years, and, as "doubt grows with knowledge" (Goethe), old persons should be less prone than the young "to that kind of fanatical certitude which provokes enmity, aggression and hasty war".

RADIUM THERAPY.

THE Manchester School has played a prominent part in developing exact methods in radium therapy whereby a uniform distribution of radiation is obtained throughout any desired volume of tissue. The first of the significant papers appeared in 1934, and others at intervals since then. Copies of many of these are now in short supply. The material in the six most important papers has therefore been rearranged and conveniently assembled in a single volume.[1]

The subject matter has been divided into two parts. The first section, comprising 46 pages, deals with the clinical aspects of treatment by moulds, by interstitial arrangements of needles, and by gynæcological applicators. The methods of calculating the total quantity of radium required and the manner in which this radium should be distributed are clearly set out and illustrated with examples.

The second section of 71 pages indicates the physical principles on which the treatment methods have been based, and is of interest more particularly to the radiological physicist and to the experienced radiotherapist who is confronted with the treatment of a lesion of a complicated shape. The use of radiography to determine how closely the desired distribution of radium containers has been achieved is discussed thoroughly.

A number of tables of assistance in various dosage calculations are included as appendices. The volume, which is well printed, provides ready access to all aspects of the Manchester techniques and will be of value to all who use γ rays.

DYING, APPARENT DEATH AND RESUSCITATION.

A MOST interesting book upon a subject not frequently writen about is "Dying, Apparent Death and Resuscitation", by S. Jellinek, and it is of interest to note that although the subject matter was gathered whilst the author was professor of electropathology at the University of Vienna, the book was written during his exile in Britain in the war years.[2] The writer has made a very detailed study of the subject of dying which he rather teutonically terms thanatology and also of the origin of the process of dying (thanatogenesis); he has also delved into the folklore associated with the subject. However, from a practical viewpoint the chapters dealing with resuscitation are of greater interest to practising doctors, and the casualty surgeons of all big city hospitals as well as all physicians and ambulance men can derive much help from this book. In cases of apparent death following electric shock the author stresses the rather startling success achieved by lumbar puncture used in conjunction with artificial respiration. He also describes his own method for artificial respiration in which the shoulder girdles are used as levers to move the thorax, and he states that by this method there is no danger of damage to the ribs or viscera as there is in the methods of Sylvester and Schafer. Advocates of the "new" rocking method of resuscitation will be interested to know that it has been the practice in central Moravia to place the apparently drowned into a barrel and rock it. In concluding, the author makes a plea for the establishment of an international information service for life-saving where all aspects of the subject could be discussed and correlated. Whilst the worth of such a service is obvious, the same could be said for services associated with all branches of medicine. Human nature, being such as it is, would force even doctors associated with such schemes to disagree, and then decisions would probably be left in the hands of others, even political arbiters.

[1] "Radium Dosage: The Manchester System", edited by W. J. Meredith, M.Sc., F.Inst.P.; 1947. Edinburgh: E. and S. Livingstone, Limited. 9¾" × 7½", pp. 134, with illustrations. Price: 15s.

[2] "Dying, Apparent Death and Resuscitation", by S. Jellinek, M.D.; 1947. London: Baillière, Tindall and Cox. 7½" × 5", pp. 272. Price: 10s. 6d.

The Medical Journal of Australia

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THE ROYAL MELBOURNE HOSPITAL AND ITS CENTENARY.

THE people of the State of Victoria will during the next few weeks celebrate the centenary of the Royal Melbourne Hospital. The event is of considerable significance to the community and most of all perhaps to the medical profession of the State, for its members more than any other group of persons have been responsible for the extent to which during the long period of years the objects of the institution have been attained in the relief of human suffering. And there is every reason why medical practitioners in all parts of Australia should make common cause with their Victorian colleagues in their rejoicing. To rejoice on the attainment of a hundredth birthday in a humanitarian undertaking is natural and especially shall we make merry if the object of our joy is something in whose conduct we share or in which we take a personal delight. But it is necessary to see the whole venture in its proper perspective, to realize, for example, that the erection of the new and modern hospital now known as the Royal Melbourne Hospital is not the fulfilment of a recently conceived idea. We shall then give credit to the right people and we shall see progress as a continuing process. Time does not stand still and as one set of human needs appear to be satisfied, others arise and demand attention. The progress of the Royal Melbourne Hospital, told in a special article in this issue by Dr. H. Boyd Graham, has been difficult (how difficult and heart-breaking to many who in the past appeared often to battle in vain, we cannot imagine) and it would be easy to fold the hands in contentment with a new hospital in being and to take no further thought for the future. But we know that to adopt such an attitude would be foolish. For our present purposes we may give consideration to some aspects of hospitals to which attention is not always paid, and then look at our hundred-year-old institution from three points of view—the past, the present and the future.

Hospitals, like other human institutions, do not consist entirely of the external forms from which they derive their names; they have other, and more important, components than the buildings which house their inmates. Hospitals have been said to possess a soul as well as a body. This idea was put forward in this journal in December, 1930, by Dr. Robert Scot Skirving in an address to *alumni* of the Royal Prince Alfred Hospital at Sydney. Basing the title of his address on an essay by the late Harvey Cushing, he spoke "on the body and soul of a hospital". The body of a hospital, the "raiment", as Cushing called it, might often count for comparatively little, for it was not always in palatial structures of stone that great discoveries had been made and the highest skill had been shown in the lessening of human suffering. The soul of a hospital, big or little, did not depend too greatly on the vastness of its buildings, the number of its inmates or its wealth, but "rather on the quality, and to a less extent *pro rata* on the quantity of its useful personal service to humanity". This service depended on those who served, on their character, their loyalty, their keenness and their perseverance. The "raiment" of the Royal Melbourne Hospital has not always been so splendid as it is at present; the hospital has not always been dignified by the title "Royal". With the passage of the years the "raiment" grew, though not without lagging, with the growth of the community and the demand for hospital services. The "Battle of the Sites" mentioned by Dr. Graham was partly in the nature of "growing pains". With the detailed history of the growth we need not concern ourselves at the moment, but one point must be emphasized. The structure, equipment and resources of a hospital provide the means for the carrying out of useful work. "Unto whomsoever much is given, of him shall much be required." The present "raiment" of the hospital has been described as splendid and this will not be denied. The obligation therefore of all who serve to give of their best in full and plenty is in like measure great.

Dr. Graham has described the growth of the hospital and has told how the present structure came into being on its unrivalled site. We can turn to the other side, the service given on the staff by successive generations of medical practitioners. Though the first patients were admitted on the opening of the hospital in March, 1848, the first medical staff was elected in July of the previous year. Dr. E. C. Hobson, Dr. Arthur O'Mullane and Dr. Godfrey Howitt were elected honorary physicians and Mr. A. F. A. Greeves, Mr. David J. Thomas and Mr. W. H. Campbell were elected honorary surgeons. Dr. Hobson died before entering on his duties and Dr. W. B. Wilmot was elected as his successor. The work of these men was not arduous, for we read that the six of them had to attend only twenty patients, but they were the first of a long line of medical officers who have fashioned the "soul" of the institution. The establishment of the medical school of the University of Melbourne in 1864 was found to have an important influence on the activities of the hospital. The late Bernard Traugott Zwar has recorded that when medical students first entered the Melbourne Hospital in 1865 certain members of the medical staff were either hostile or indifferent to their interests. For a while hospital and university seemed to be at cross purposes. In 1870 the Committee of the hospital, urged by a medical member, Robert Knaggs, carried a motion

stating that it was both "expedient and indispensably necessary" that clinical lectures should be delivered by members of the honorary staff to students attending the practice of the hospital and that the honorary staff should report upon the best mode of carrying out the proposition. Apparently hostility and indifference continued, for in 1875 the Committee found it necessary to pass a rule stating that every physician and surgeon should give special clinical instruction to students in attendance on him and should at least once a week deliver a clinical lecture which should be open to all students of the hospital. On the other hand the Committee did not receive from the University the support which its efforts merited. The details of the unavailing efforts to secure cooperation need not be recorded here, but it should be noted that it was not until the establishment of a new university curriculum for students in 1887 that a satisfactory state of affairs was reached. In this difficult time there were probably faults on both sides, but whether this was so and to what circumstances or to whom the faults were due does not concern us. The point is that the happenings must have had a retarding influence on the development of the character and efficiency of the real work of the hospital. With the appointment of Dr. John Williams as lecturer in clinical medicine and Mr. Thomas Fitzgerald as lecturer in clinical surgery an improvement began to take place. With the establishment in 1915 of the Walter and Eliza Hall Institute of Research in Pathology and Medicine (recently renamed the Walter and Eliza Hall Institute of Medical Research) a great forward step was made. Everyone will agree that the influence of this institute on the clinical work of the hospital has been immense. When we look at the past history of the Royal Melbourne Hospital in the aspect with which we have chosen to deal, we can declare with confidence that what has been created is in the best tradition of medicine and hospitals. We would go further and suggest that in addition there has been created a tradition peculiar to the institution itself. To this end many persons of varying talent but with singleness of purpose have made contribution. They have sought for truth, bringing their wide experience to a central focus in their common meeting ground of ward and laboratory. Included among them were men richly endowed and generous with their gifts of heart and mind—men such as Harry Brookes Allen, William Boyd, Thomas Fitzgerald, David Grant, Henry Maudsley, William Moore, George Adlington Syme, Richard Rawdon Stawell, John Williams and Bernard Traugott Zwar. With men of such calibre as ensamples of keenness and devotion it is natural that part of the centenary celebrations is to take the form of a series of meetings at which papers on clinical medicine and surgery will be presented.

The papers to be presented at the scientific sessions cover a wide field in medicine and surgery and among the speakers will be Sir Hugh Cairns, of Oxford, and Dr. William Evans, of London. Dr. Evans will lecture on heart sounds, on heart murmurs and on heart pain. The subject of the lecture by Sir Hugh Cairns is not stated in the provisional programme. Those who attend will include ex-students of the Royal Melbourne Hospital as well as other medical graduates who will be welcomed as visitors. They will have ample opportunity of seeing for themselves the new and magnificent hospital which has made certain dreams come true. They will realize the wealth of opportunity presented for the study of disease, for the training of medical students and nurses and for the treatment of the sick. Reference to opportunity makes us think of the future. At the outset we remarked that time does not stand still, that progress must continue. If there is no progress, there will be regression. But this is unthinkable; tradition and the inquiring spirit of the age make it so. One fact which augurs well for the future is the recent creation of a clinical research unit, under the control of Dr. Ian Wood, of the Walter and Eliza Hall Institute of Medical Research. The note for the future is one of sure and certain hope.

Current Comment.

THE MECHANISM OF PHAGOCYTOSIS.

TREATMENT of the ills to which the flesh is heir occupies the time and thought of the great body of the medical profession. Studies during training give the doctor a knowledge of the functioning of the normal body, and a picture of the diseased organs after death. This is the basis of his understanding of the process of disease which has caused the death of an individual; real knowledge of the mechanisms involved, however, is limited.

The spreading inflammation in lung tissue produced by the multiplication of the capsulated pneumococcus has long served as a type of acute infection easily accessible for study, and it is usually taught that recovery depends on two factors—one the phagocytic leucocyte which ingests the organisms, the other the chemical antibody which alters the surface of the bacterium, making it susceptible to ingestion by the phagocyte. Antibodies appear in the body fluids four to five days after infection takes place, in response to the stimulus of absorbable antigenic fractions from organisms during their early multiplication in the incubation period of the disease. Test tube experiments with mixtures of living leucocytes and organisms in a fluid medium show little phagocytosis unless antibody is present to sensitize the cocci to ingestion by the cells, suggesting that the two factors are interdependent.

The advent of the sulphonamides brought a new weapon to the therapeutic armamentarium, and a new tool to the laboratory worker, leading to a greatly increased study of the metabolism of bacteria against which these drugs are effective. D. D. Woods[1] evolved an hypothesis that the action of sulphonamides depended on the fact that the drug could compete successfully against the organism for substances of the nature of para-aminobenzoic acid, essential for its metabolism, since it cannot synthesize them for itself. This was soon substantiated, and a great deal of information was gained about the factors concerned in the action of the drug.

Now comes from W. Barry Wood, junior, and his co-workers a study which greatly advances our knowledge of the process of phagocytosis, and brings to light new facts. He has studied in the lung of the rat pneumonia, produced by the pneumococcus,[2] and by the capsulated organism known as Friedländer's bacillus.[3] First he obtained a clear picture of the untreated disease, then a picture of its modification by the use of sulphonamides, dealing with both the cellular and humoral factors of recovery. He found that the spread of the disease was

[1] *The British Journal of Experimental Pathology*, Volume XXI, 1940, page 301.
[2] *The Journal of Experimental Medicine*, Volume LXXXIV, 1946, page 365.
[3] *The Journal of Experimental Medicine*, Volume LXXXVI, 1947, page 239.

achieved by multiplication of the organisms at the "edge" of the area in which œdema fluid filled the lung alveoli, and behind which the inflammatory cells and phagocytes accumulated. He found the surprising fact, however, that he could see phagocytosis going on long before antibody could be demonstrated in the tissue fluid or in the blood serum. He evolved an ingenious technique to test the accuracy of this observation, and proved that leucocytes when in contact with a suitable surface, such as the alveolar wall, can as it were "pin" the organism there, flow over it and ingest it. This will also happen when a thin film of organism and leucocytes is spread on moistened blotting paper or sterile tissue slices, but will not take place on glass surfaces. This is an entirely new concept in the mechanism of phagocytosis, and the admirable photographs with which Barry Wood's paper is illustrated leave little doubt in the mind as to the truth of his statements. Also clearly seen are the mechanisms of spread of the infection, whereby the œdema fluid, containing organisms and a minimum of cells, flows over into adjoining alveoli, while lymphatics, through which it was formerly thought the bacteria travelled, seldom exhibit bacteria in the lumen. Wood does not suggest, of course, that antibody has no part to play in the later stages of the pneumonic process, but he does show that the defence mechanisms in operation in the early stages can function in its absence.

HYPERVENTILATION AS A CLINICAL SYNDROME.

THE effects of hyperventilation on bodily function have been and still are of great interest to the physiologist, and therefore to the practising physician. But, because it is common, and because common things are as worthy of study as the rare ones, it is no doubt still neglected. G. L. Engel, E. B. Ferris and Myrtle Logan, working on a specific research on the subject, have produced a condensed survey, in which they begin by stating that the symptoms of hyperventilation are frequently overlooked.[1] They go on to remark that patients seldom complain of overbreathing, and seldom exhibit tetany, which, though the best known manifestation, is one of the least common. For those who read medical novels it may be remarked that the young physician in "The Citadel" was perhaps fortunate that a wealthy patient with hysterical hyperventilation supplied the diagnosis so neatly with a textbook attack of tetany. These authors point out that by far the commonest cause of the hyperventilation syndrome is of psychogenic origin. There may be something about hospitals which predisposes to attacks within their walls, for there must be few experienced clinicians attached to large hospitals who have not witnessed such attacks, not only among patients, but even among members of the junior nursing staff. This variety of hyperventilation is not unusual in states of anxiety, and Engel and his associates mention a number of psychological mechanisms which may activate the process. In other spheres it may be important also, as in reactions to certain drugs, like the salicylates, and in the anoxia of high altitudes.

The authors point out that the symptoms are the same in essence, though not, of course, in degree, whatever the cause. Numbness and tingling of the hands and feet are felt, also in the face, which is not a usual site for this sensation, a buzzing is complained of in the head, and consciousness is reduced in degree to various extents. This may amount only to a giddy or light-headed feeling, or the patient may feel faint, though actual syncope is rare. The vision may be blurred, the mouth dry, the muscles may be stiff, and true tetany may follow. It is not usual for patients who have involuntary attacks of hyperventilation to notice this feature, but they are conscious of great exhaustion, which is also a striking sensation felt by those experimentalists who have voluntarily produced overbreathing in themselves. Reduction of the level of consciousness may release in the anxious patient a variety of affective mechanisms, including obviously hysterical manifestations. The approach to the problem in this research was to investigate the blood chemistry and the cerebral changes as registered in encephalographic tracings in volunteer subjects of hyperventilation. The effect of various factors such as posture and the administration of various drugs was studied. From the material obtained by these extensive investigations these workers have come to some definite conclusions. They consider that there are two components to the symptomatology of hyperventilation, those related to disturbances of consciousness and those concerned with tetany. Electroencephalographic studies showed that the former were related to changes in the electric activity of the cerebral cortex. These changes could be modified by many other physical and chemical factors. They note in particular that reduction in consciousness can be well coordinated with the degree of slowing of the electroencephalogram. Such slowing is correlated with a rapid reduction in the content of carbon dioxide in the arterial blood, or of sugar in the blood, or of oxygen in the inspired air. It also occurred more conspicuously in the erect posture, and after the administration of vasodilator drugs. The electroencephalographic changes were not at all affected by the injection of calcium salts or nicotinic acid during hyperventilation. Tetany appeared to be of peripheral origin, so far as the manifestations were concerned, as were also numbness and tingling, though the relation of these to tetany was uncertain.

A clearer understanding of the mechanisms involved is of interest, and especially since the condition under investigation can be accurately produced experimentally by volunteers. Some of the queer attacks complained of by nervous and anxious people, particularly those of the hysterical type, are without a doubt due to this cause, but as the clue is usually not given to the medical attendant, the patient being generally unaware of it, he must supply it himself by deductive reasoning and a little recollection of physiology.

[1] *Annals of Internal Medicine*, November, 1947.

CONGENITAL MORPHINISM.

CONGENITAL MORPHINISM is a rare cause of convulsions in the newborn. It has been recognized since as far back as 1875, but it is so rarely mentioned in the literature that the report of a case is noteworthy. Meyer A. Perlstein[1] has discussed a female infant who was born by Cæsarean section on July 9, 1941, the mother being a known morphine addict, aged thirty-four years, who was at that time taking intravenously an average of 10 grains of morphine a day. The child was apparently normal at birth, but on the third day of life she became irritable and restless, vomited and began passing liquid stools, though she still took her food. By the end of the fourth day, symptoms were exaggerated and generalized tremors appeared. She lost weight, she slept fretfully and when disturbed held her breath and on occasion had generalized clonic convulsions. Extensive investigations yielded no abnormal findings. However, the *vernix caseosa*, which had by chance been preserved for other reasons, was found to contain morphine. Sedative treatment was begun. The administration of phenobarbital, one-eighth of a grain every four hours, rapidly allayed all symptoms. The child made satisfactory progress, though the mother noticed occasional tremors during the first month after birth; at the end of eight weeks the phenobarbital was tapered in dosage and finally stopped. Subsequent development was normal. Perlstein, who has included a review of the relevant literature in his report, states that the infant develops addiction from morphine passed through the placenta, but points out that the former belief that morphine was excreted in the mother's milk has been disproved. Thus the idea that breast feeding aids in treatment is fallacious; emphasis in treatment is now placed on sedative drugs—in this case a barbiturate—and with success.

[1] *The Journal of the American Medical Association*, November 8, 1947.

Abstracts from Medical Literature.

PATHOLOGY.

Endothelial-Cell Sarcoma of Liver following Thorotrast Injections.

H. EDWARD MACMAHON, ALBERT S. MURPHY AND MARGARET I. BATES (*The American Journal of Pathology*, July, 1947) report a case of a patient who had been given thorotrast for the visualization of the liver. With the aid of this diagnostic procedure, combined with serological tests, it was possible to make an accurate diagnosis of hepatic syphilis with gumma. Following specific therapy, the patient made a clinical recovery and for twelve years lived a reasonably normal life. At the age of seventy years death came suddenly. Autopsy findings confirmed the diagnosis of syphilis and in addition revealed a primary hæmorrhagic endothelial-cell sarcoma of the liver, the source of fatal hæmorrhage, and very widespread irradiation injury affecting particularly the liver and hæmatopoietic system. Evidence is produced from a study of this case to support the debatable contention that thorotrast in sufficient quantities as a radioactive substance is injurious. Evidence is also produced to show that thorotrast, like other radioactive substances, in sufficient time may act as a sarcogenic agent.

Gelatin Nephrosis.

OLAF K. SKINSNES (*Surgery, Gynecology and Obstetrics*, November, 1947) reports the post-mortem findings in 23 subjects who had received intravenous gelatin therapy and who expired as a result of medical and neoplastic disease or from complications of therapeutic surgical measures, as demonstrating the ætiological role of gelatin in the pathogenesis of renal hydropic changes morphologically similar to those produced by the intravenous injection of sucrose. The morphology of the renal lesion produced by gelatin is described and compared with that of sucrose nephrosis. Gelatin nephrosis is shown to be a reversible change occurring within half an hour after the intravenous injection of gelatin and disappearing within one hundred and twenty hours following the last injection. Studies of the effect of the renal lesion on renal function are reported as inconclusive, but two suggestive cases are discussed, one showing diuresis and the other oliguria following the intravenous administration of gelatin. Caution is suggested in the use of this substance in patients exhibiting previous renal impairment. Attention is directed to the possible role of gelatin in promoting circulatory disturbances, and three cases are reported as suggesting that gelatin is a potential precipitating factor of coronary occlusion and vascular thrombosis in the presence of circulatory disturbances and vascular disease.

The Histopathology of Acute Mumps Orchitis.

EDWARD A. GALL (*The American Journal of Pathology*, July, 1947) reports the study of testicular and epididymal tissue obtained from 76 subjects of acute mumps orchitis (75 for biopsy and one at autopsy). In all cases testicular tissue was available. In eighteen cases there was material from the appendages and in two (three specimens) from the epididymis. Material was obtained during the first five days of symptoms in all but one case. Considerable variation was evident in the character and extent of the lesions in the testis, but it seemed that a developmental trend could be detected. From early œdema and a scant perivascular lymphocytic exudate the process progressed to a diffuse lymphocytic infiltration of the interstitial tissue with focal hæmorrhage and pronounced destruction of germinal epithelium, with plugging of the tubules by epithelial debris, fibrin and polymorphonuclear leucocytes. The intratubular lesion remained focal in most instances, but in a few cases every tubule in a given section was involved. Evidence of collagenization was elicited only in the one late case in which material had been obtained on the eleventh day. Inflammation of the testicular appendages and of the epididymis remained confined to the connective tissue elements and, with a single exception, was wholly lymphocytic in character. Epithelial elements were unaffected in these structures.

Hæmolytic Anæmia Associated with Malignant Disease.

DANIEL STATS, NATHAN ROSENTHAL AND LOUIS R. WASSERMAN (*American Journal of Clinical Pathology*, August, 1947) state that Hodgkin's disease, chronic lymphatic leuchæmia, reticulo-endotheliosis, metastatic carcinomatosis, sarcoma of the spleen, myelogenous leuchæmia, lymphosarcoma, giant follicular lymphoblastoma and Boeck's sarcoid are occasionally complicated by symptomatic hæmolytic anæmia. The blood picture and bone marrow in such cases may reflect changes caused by both diseases. Spherocytosis and increased fragility of erythrocytes in hypotonic salt solution occur in about 50% of the cases. The pathological changes in the spleen are variable. In some cases "arterial" or active hyperæmia is present; in others the specific changes of the underlying disease are observed; in certain instances "non-specific" alterations, such as reticulo-endothelial hyperplasia, erythrophagocytosis and myeloid metaplasia, are seen. The reason for this variation is not clear; it is not dependent upon any of the hæmolytic findings. The unpredictable effect of, and indications for, various forms of therapy are discussed. The occurrence of spontaneous remission is pointed out. Summaries of ten cases are given illustrating the clinical and hæmatological findings and response to treatment.

Gargoylism.

REUBEN STRAUS, REUBEN MERLISS AND RAYMOND REISER (*American Journal of Clinical Pathology*, September, 1947) state that within the past twenty-five years there has been recognized and accepted as a specific entity a characteristic grotesque malformation of the body believed to be associated with a lipoid dystrophy variously referred to as gargoylism, lipochondrodysplasia, Hurler's syndrome, osteochondrodystrophy and *dysostosis multiplex*. The disease is relatively uncommon, only about 65 cases having been reported to date, and of these only five subjects have come to autopsy. The authors report a case of gargoylism together with detailed clinical, X-ray, post-mortem and chemical studies. The literature on the subject has been summarized and analysed. Evidence has been submitted to suggest that the deformities may be produced by a disease of collagenous connective tissue, chiefly affecting the fascia and ligaments, rather than by an abnormality of bony growth as previously accepted. It is believed that abnormalities are probably initiated by congenital factors, chiefly because of the high familial incidence of the disease. It has been shown that lipoidosis is not a constant feature of the disease entity. When present, however, it is found in the brain and in the reticulo-endothelial system, as in other idiopathic lipoid dystrophies. Chemical analysis of the tissues in this case revealed a significant increase in lipid content of the lymph nodes, but not of the brain, liver or spleen. The increased lipid was, by exclusion, simple fat probably in complex protein combination. The fact that it was not a phospholipid, cerebroside or cholesterol separates this disturbance from the other idiopathic lipoid dystrophies. No relationship was established between the genesis of the physical abnormality and the reticulo-endothelial disease.

Deaths following Use of Abortifacient Paste.

WILLIAM KULKA (*American Journal of Clinical Pathology*, September, 1947) describes the autopsy findings in two cases in which death followed the injection of an abortifacient paste. In one instance death occurred two and a half months after the attempted abortion. Necrosis of the uterine wall, parametrial abscesses and generalized peritonitis were found. The second patient died suddenly of pulmonary embolism within a few hours after an attempt to cause abortion by intra-uterine injection of the paste. The emboli were composed of fatty material and particles from the damaged chorionic villi. There was necrosis of some of the villi and vessels of the uterine wall, but no apparent changes in the embryo or the embryonic sac. The presence of a pasty material was demonstrated by the technique used routinely for the demonstration of fat, but the staining reaction was different from that of fat.

MORPHOLOGY.

Effect of Œstrogens on Mitotic Activity in Hypophysis of Ovariectomized Rats.

T. E. HUNT (*The Anatomical Record*, February, 1947) states that mitotic activity may be increased in the anterior lobe of the hypophysis of ovariectomized rats between forty-one and ninety-eight hours after injections of œstrogens. In order to equal the number of mitoses found in the hypophysis of normal rats in the post-œstrous phase of the sexual cycle, it is necessary to inject 250 to 300 rat units of "Theelin" or "Progynon-B" seventy-two and forty-eight hours before death. In animals three months of age such injections result in an average appearance of thirty mitoses per square millimetre of sections three

microns in thickness. Larger amounts do not cause a further increase. With smaller injections the number of mitoses is proportionally smaller. The injection of 2·5 rat units, which is sufficient to cause an œstrous response, does not cause an appreciable increase in mitotic activity. As the animals become older, the pituitary cells become increasingly refractory to the mitotic stimulating effect of œstrogens. There are four to eight times as many mitoses in animals aged three months as in those aged ten months receiving an equivalent amount of hormone.

Fibrillar Structure of Bone.

E. B. RUTH (*The American Journal of Anatomy*, January, 1947) advances our knowledge of the basic bone substance by an investigation, using a special technique, on sections made from the middle third of the diaphysis of femurs taken from dissecting room subjects. This investigation does not confirm the deductions of Gebhardt and others concerning the arrangement of fibrillæ in bone. On the contrary, it shows the fibrillæ to have a simpler arrangement that more readily yields itself to the understanding of bone development and repair. Osseous tissue is made up of fibrillæ masked by a granular interfibrillar substance. Fibrillæ are laid down in alternating lamellæ of compactly arranged circumferential fibrillæ with interfibrillar spaces small or absent, and diffusely arranged radial fibrillæ with wide interfibrillar spaces. Fibrillæ of the alternating bands bear an orthogonal relationship to each other, and lie in a transverse plane in relation to the long axis of a long bone. There are no longitudinal fibrillæ. Fibrillæ can be stained differentially with orcein and picro-fuchsin.— Radial fibrils of the diffuse lamellæ are stained purple with orcein and orange to yellow with picro-fuchsin. Circumferential fibrils of the compact lamellæ are not stained with orcein, and are stained red with picro-fuchsin. Lacunæ are more intimately associated with the compact lamellæ in general. Canaliculi pass through the fibrillæ of both bands, from the lacunæ or directly from the Haversian canal itself.

Conduction System in Moderator Band.

R. C. TRUEX AND W. M. COPENHAVER (*The American Journal of Anatomy*, March, 1947) studied histologically with various stains the moderator band of the right ventricle from the hearts of several mammals including man. The investigation was undertaken to determine, firstly, the structural characteristics of the Purkinje fibres concerning which contradictory conclusions have appeared in the literature, and, secondly, the relative proportions of cardiac muscle, Purkinje fibres, and connective tissue in bands of different sizes. Purkinje fibres were found in all sheep, pig, calf and beef bands, and species differences in arrangement and staining reactions were noted. In man, Purkinje fibres were identified in 14 of the 20 bands examined, and a continuity with cardiac muscle fibres was observed. The claim by some investigators that Purkinje fibres of characteristic type do not exist in man, and that there is no continuity of Purkinje and cardiac fibres even in the ungulates is thus not substantiated by this study. The Purkinje fibres of the ungulates are more than twice the diameter of cardiac muscle fibres. In man most of the Purkinje fibres have a smaller diameter and are more nearly the size of the cardiac muscle fibre. It appears from this study that both the cardiac and Purkinje fibres enlarge with the growth of the heart. Small transitional or intermediate-sized fibres are frequently observed in man. Such fibres are the only type observed in the sections from the cat and monkey hearts. In four of nine human bands, and six of ten human interventricular septa, the Purkinje fibres were well differentiated from the adjacent cardiac muscle fibres with Best's carmine method. The intrafibre glycogen content offers an ideal criterion for determining Purkinje fibres if stainable glycogen is present. A relatively large artery courses through the moderator band to the anterior papillary muscle. Measurements showed that the diameter of the vessel is not correlated with the size of the band. The wall of the vessel contains both longitudinally and circularly arranged smooth muscle fibres. Several large nerve fascicles traverse the band. The authors observed many delicate pale-staining nerve fibres in initimate contact with the surfaces of the Purkinje fibres, but did not see any specialized terminations. They could follow fine varicose fibres from their perivascular plexis to small club-shaped terminals on the surface of cardiac muscle fibres. From measurements of a series of specimens in each species it was found that the smaller bands possessed little or no cardiac muscle, whereas larger amounts of cardiac muscle were usually encountered in the large bands. The small bands in which no cardiac muscle is present serve solely as conduits for most of the right branch of the auriculo-ventricular bundle, the artery of the moderator band, and large fascicles of nerve fibres. Of the band elements measured, cardiac muscle was the most variable, while Purkinje tissue was the most constant.

Regenerating Nerve Fibres.

J. T. AITKEN *et alii* (*Journal of Anatomy*, January, 1947) conclude that the growth of new nerve fibres in regenerating nerves is under the control not merely of central influences, but of three sets of factors, namely, (i) the cell body and central stump, (ii) the condition of the pathway along which the fibre travels, and (iii) the connexions which it makes with an end organ.

Origin of Sympathetic Ganglion Cells.

W. S. HAMMOND AND C. L. YNTEMA (*The Journal of Comparative Neurology*, April, 1947) report the results of experiments on the neural crest and consider the respective roles played by it and the neural tube in the formation of the sympathetic system in the trunk of the chick. In studies on neurogenesis, it is generally accepted that the afferent neurons of posterior root ganglia are derivatives of the neural crest, but it has been debated whether the neural crest may also give rise to sympathetic ganglion cells. Some investigators have concluded that these latter cells migrate from the ventral part of this neural tube. In the present investigation, neural crest was removed bilaterally from the thoracic and lumbar regions of the chick. The results of these operations indicate that the peripheral sympathetic neurons in the thoracic and lumbo-sacral regions arise from neural crest of the region. The chromaffin cells of the suprarenal medulla are also absent after appropriate removal of neural crest. The formation of cortical cords of the suprarenal appears to be independent of the presence of preganglionic fibres or medullary constituents. Preaortic chromaffin cells arise from neural crest. The column of cells in the cord which give rise to the preganglionic sympathetic fibres differentiate in the absence of the neural crest and its derivatives. The preganglionic fibres emerge from the neural tube and complete an essentially normal pattern for a trunk sympathetic system devoid of peripheral sympathetic neurons. There is no evidence that cells migrate from the preganglionic column or ventral neural tube to form neurons of the sympathetic ganglia. Injury to the preganglionic centre along with absence of sympathetic ganglia is reflected in interruption or absence of the paravertebral trunk for one or more segments. Longitudinal migration of sympathetic rudiments into the area operated on may occur for varying distances. This movement may proceed into the anterior or posterior ends of the region of operation. The extent of the migration in animals subjected to operation may depend on the presence of a fibrous pattern formed by preganglionic fibres. There is no evidence that this is a feature of normal development. Extravasations of the motor columns as a result of the operative procedure do not contribute to the formation of the sympathetic system in the trunk of the chick. Bipolar cells may be found in the spinal nerves, but they do not appear to be of importance to the problem. The enteric plexuses and Remak's ganglion are not obviously affected by the removal of thoracic and upper lumbo-sacral neural crest.

Circulus Arteriosus of Willis.

LAMBERT ROGERS (*Brain*, June, 1947) has carried out injection experiments on the cadaver, studied arteriograms in the living, and made observations on a working scale model, as a result of which he concludes that the circle of Willis is a constant, albeit an irregular, anastomosis between the vertebral and carotid arterial systems, comparable with anastomoses between main arterial channels elsewhere in the body. Under physiological conditions it does not permit a mingling of the blood streams in the main vessels across which it lies. It should not therefore be regarded as a distributor or equalizing station or booster mechanism for the cerebral blood supply. Its value is potential rather than actual, because like all anastomoses it provides a by-pass capable of opening up, should one of the main channels across which it lies become obstructed. Occlusion in the neck of one carotid artery for aneurysm on its intracranial course is effective in reducing blood flow within the aneurysmal sac, whether this lies below or above the level of the circle, and constitutes a true Hunterian operation of distal proximal ligature. In a series of cases of leaking cerebral aneurysm causing subarachnoid hæmorrhage, carotid ligation has been performed with success, bleeding being arrested and symptoms relieved.

Special Article.

"THE UNIMAGINABLE TOUCH OF TIME": THE CENTENARY OF THE ROYAL MELBOURNE HOSPITAL.

THE Royal Melbourne Hospital stands to the north-west of the city, ten storeys high, beside the road leading to Sydney. It is an easy and a pleasant walk across the adjacent university grounds to the buildings of the Medical School where the students learn, in lecture theatres, dissecting rooms, museums, libraries and laboratories, the academic subjects that enable them to apply the lessons of science to the clinical problems that await solution in the hospital.

Elsewhere and in humbler quarters the doors of the Melbourne Hospital were first thrown wide open to "succour unhappiness" on March 15, 1848. With indomitable earnestness and courage, successive generations of committee members, managers, doctors and nurses have striven to keep abreast of the ever-growing demands. They have kept prominently before them the provision of the highest possible quality of professional service and the best of accommodation and equipment. The attainment of these objectives has been fraught with difficulty on innumerable occasions. The Hospital has always attracted capable people to serve it and the support of those with the necessary superfluous wealth for its costly building and maintenance funds. Since the University Medical School was founded in 1864, clear-thinking leaders have battled to bring the Hospital close to the university as the fundamental nucleus of a great community medical centre. On this centenary occasion it is fitting that we should heartily congratulate those at present in charge of the affairs of the Hospital on the recent triumphant accomplishment of the first and most essential step of this project by rebuilding the Hospital on the Parkville site. The Women's Hospital is already near the university, and it may be predicted with confidence that a fine new children's hospital will soon arise not far away.

The story of the Melbourne Hospital is a noble one and it is full of inspiration for us all. The persons rather than the buildings, the deeds rather than the years, and the thoughts and feelings rather than the chronological details are the highlights of the saga.

The Early Days.

Batman's little village on the banks of the Yarra became the principal settlement in *Australia Felix* when, in March, 1837, the main streets, one chain and a half wide, were laid out in a rectangular pattern by Robert Hoddle, the senior officer of the Survey Department, who came from Sydney for that purpose with Lieutenant-General Sir Richard Bourke, the Governor of New South Wales.

A series of land sales, two of them in 1840, placed portions of the Port Phillip district of New South Wales into private possession and hundreds of thousands of pounds of capital into the Sydney Treasury. A drought in 1841 reduced the price of the sheep that survived to sixpence or a shilling a head. The settlement nearly foundered, but by the boiling down of sheep for tallow the value per sheep rose to eight shillings and bountiful rains came later, but not too late. Optimism succeeded depression and the fortunate in the small community had learned to pity the miserable, especially those who were old, destitute or sick. The Government in Sydney was remote and indifferent to the sufferings at Port Phillip settlement; a ship coming and going every three weeks was the sole communicating link. No ship could come direct to Port Phillip without calling at Sydney for customs purposes, increasing the cost of its precious contents. Ten auctioneers were in business in Collins Street selling land and goods of pioneers to pioneers.

In the early days a two-storey house was built for John Batman on the south-east corner of William and Collins Streets, where now the great Australian Mutual Provident Society's headquarters building stands. This brick house was placed temporarily at the disposal of the doctors for use as a hospital. Unfortunately Batman died in 1839, but a government regulation had been obtained on March 1, 1839, authorizing the establishment of a communal hospital on a site to be selected and guaranteeing a small subsidy of £300 if a similar amount was first raised privately. After Batman's death the temporary hospital building became the chief auction mart in which the two land sales of 1840 were conducted and where the first Superintendent of Port Phillip District, C. J. La Trobe, had to purchase the land at Jolimont on which he erected the house he had brought with him in sections from Europe. Dr. Patrick Cussen, the government doctor, had a miserable, small hospital behind the shack in Collins Street, which was the temporary gaol of the settlement pending the completion of the building at Pentridge already then undergoing construction. There was also some provision made for the sick of the Jewish community.

In 1841 the Hospital Provisional Committee rented for temporary use "a small brick cottage in Little Collins Street" and later moved "to more spacious and two-storied premises in Bourke Street nearly opposite the now St. Patrick's Hall". This house and perhaps both of them probably belonged to John Pascoe Fawkner at some time or other. "The accommodation was most inadequate and inconvenient, but it had to be endured as best it could." In 1843 and again in 1844 applications to the Government for a site failed and the subscription list languished at £215.

As the direct outcome of a private meeting at Dr. Palmer's house, at Richmond, towards the end of 1844, at which Superintendent La Trobe and Resident Judge Jeffcott were present, new and more influential representations were made to Governor Gipps and a site was soon promised as well as a subsidy of £2000 to be supplied in instalments. From this stage Dr. Palmer and his committee of magistrates, clergymen and medical colleagues did not let any grass grow under their feet. They formed a Hospital Commission to select a site, to raise funds and to establish the Hospital. At least six sites were taken into consideration, but, after the choice had been narrowed to two, a stalemate was reached. Dr. Palmer was keen on the Haymarket site on the north-east corner of Swanston Street and Flinders Street and approval was obtained. An influential section of the Commission disagreed, and, at a public meeting, the Haymarket site was not favoured, but the north-east corner of Swanston and Lonsdale Streets was selected on the motion of John Pascoe Fawkner, seconded by Edward Curr. It is of great interest to note that Saint Paul's Cathedral now stands on the rejected Hay and Corn Market site.

Dr. Palmer seems to have taken this upset very well, for on March 20, 1846, as Mayor of Melbourne, he laid the foundation stone of the Melbourne Hospital on the site it was to occupy for nearly one hundred years. It was a great day in Melbourne as the function was combined with a similar ceremony performed by Superintendent La Trobe for the first government bridge over the Yarra at Swanston Street. All the details of this bridge and hospital procession with its civic, masonic and military pomp and speech-making have been preserved for us by Garryowen in "Chronicles of Early Melbourne".

The two-storeyed hospital was built facing Swanston Street and it was opened on March 15, 1848, with ten beds, increased to twenty by the end of the year. The first President was His Honour the Superintendent C. J. La Trobe. The two Vice-Presidents were His Honour Judge William a'Beckett and His Worship the Mayor of Melbourne, Henry Moor. The two Trustees were Captain William Lonsdale (Sub-Treasurer of Port Phillip District) and Edward Eyre Williams (later Judge of the Supreme Court of Victoria and a Knight Bachelor). The Committee of Management also included Dr. J. F. Palmer and fourteen other outstandingly distinguished citizens; so the new hospital started off as it was to continue through the years, with a committee of competent and prominent citizens of Melbourne.

Looking back upon the election of the first honorary medical staff held on July 15, 1847, we find the initiation of a most unfortunate procedure which marred the affairs of the public hospitals until forty years ago. The medical staff was elected by subscribers with newspaper publicity, public touting and vulgar display. The newspapers published lists of candidates and their claims for appointment and also lists of qualified voters. "All gentlemen declared to be legally qualified medical practitioners by the Port Phillip or Sydney Medical Boards were to be deemed eligible as candidates."

In spite of this crude system of election, the public fortunately obtained the honorary services of the cream of the profession on the first occasion, though unfortunately the young but brilliant Dr. E. C. Hobson died before he took up his appointment and his place was taken by the Coroner, Dr. W. B. Wilmot. The other two honorary physicians were Dr. Arthur O'Mullane and Dr. Godfrey Howitt. The three honorary surgeons appointed were Mr. A. F. A. Greeves, Dr. David J. Thomas and Mr. W. H. Campbell.

In September, 1847, the rule concerning staff appointments was replaced by the following:

> That all persons shall be eligible for the offices of Physician or Surgeon respectively to this Hospital who shall hold a Physician's or Surgeon's Diploma

from some University or College of the United Kingdom of Great Britain and Ireland or from any foreign university or academical body empowered to grant medical degrees.

It is of passing interest to note that at that time there were some forty-seven doctors practising in the district and that the population of Melbourne was about 30,000 persons. By a strange coincidence Prince's Bridge was opened on November 15, 1850, in association with the Separation Day procession, news having arrived of Royal Assent to separation of the newborn Colony, Victoria, from the Mother Colony, New South Wales. Another item of interest is that Bishop Perry arrived just before the opening of the Melbourne Hospital with the news that the Church of England authorities in Great Britain had created Melbourne a city to give it a right to a bishop. Unfortunately he had mislaid the documents, and the necessary act creating Melbourne a city was passed by the New South Wales legislature later in 1848, marred by the indignity of refusing His Worship the Mayor of the new city the right to the title Right Worshipful, as used in Sydney, though this stigma was removed by 1851. The Melbourne Hospital was incorporated and operating before Melbourne was *de jure* a city and before the Colony of Victoria was born. It is of historical interest to record that it was originally decided to admit both contributing and non-contributing patients, the directors to have the power to admit poor persons gratuitously to the benefits on being satisfied of their inability to contribute to their maintenance. On numerous occasions since the question of provision for contributing patients has been raised in varying guises from acceptance of contributions up to bed cost, to the community hospital proposals of the present day for provision of public, intermediate and private hospital facilities.

The Fifties.

The event of outstanding importance in the fifties was the discovery of alluvial gold, which attracted world interest to Victoria within a year of separation and led to a frenzied rush of all kinds of people eager to get rich quickly. The tenor of life in Melbourne was disrupted and soon wealth abounded, to be flung about in wild living and plenty of hard-drinking unruliness. Many fell by the wayside and needed public assistance, which was readily supplied. The effects of this social state of affairs are reflected in the annual reports of the Melbourne Hospital. Irregular and disorderly behaviour, filth, squalor and destructiveness created problems requiring regulations when the duties of house steward, matron and house surgeon were defined; members of the honorary medical staff had to recommend the discharge of patients on grounds of that description; renovations of wilful damage represented formidable items of preventible expenditure. The housing problem was acutely felt and insufficient protection from Melbourne's proverbial vagaries of climate led to ever-increasing demands for entrance to the sheltering haven of the public hospital. We note with surprise that the most distinguished gentlemen in the Colony met solemnly for many years every Wednesday morning to make decisions concerning the acceptance or refusal of the recommendations of individual "governors" proposing that individual "deadbeats" should be patients of the hospital; though it was conceded that the doctors could accept the patients in emergency on other days, subject to the confirmation of the Committee at the next meeting. These zealous Committee members also had the right to discharge any patient at any time to make room for others. There were times when, for months on end, the Committee met daily to cope with the details that became increasingly intricate and numerous. The explanation was, of course, that the young community was isolated and inexperienced in social welfare work. Fortunately the Melbourne Hospital was already launched before the gold rush; otherwise its affairs would have been in the keeping of smaller fry and might not have been handled so firmly or so capably. In the role of committee-men of the Melbourne Hospital, the same people made recommendations to the City Council and to the Government and also acted on the recommendations as councillors and leading members of the legislature and the judiciary. Thus it was possible to add a centre block and a west wing, developing a two-hundred-bed hospital in a decade with an enormous expansion in receipts and expenditure.

There are many items in the annual reports that raise a smile nowadays. Dumping people about to die to save funeral expenses was a fraudulent practice in the early years that worried the Committee for a number of reasons. It was contrary to European custom for hospitals to accept incurable or dying patients, but the concession was yielded locally on humane grounds; the extra deaths spoiled the mortality statistics which could not stand the strain; extra work of an unproductive nature was created for the few permanent officers; and the undertakers were claiming an unreasonable proportion of the Hospital's income for services rendered. Several attempts were made by the Coroner to get juries to sheet home to the perpetrators some guilt for the deaths arising out of the removal of the patients to the hospital, but the juries obdurately continued to return the usual verdict, "Died by the visitation of God", "the evil therefore remains unchecked"! The undertakers were defeated of some of their charges by the engagement of a hospital mortuary attendant, doubtless the forerunner of Arthur ——, known to many of us not so very long ago.

Then there was the matter of the steward and collector, whose conduct in 1853 the Committee felt compelled to denounce. "On being called upon to render an account of monies received by him on behalf of the Hospital he suddenly left Melbourne for England, via Sydney, leaving everything under his charge in the greatest possible confusion." Doubtless there have been other defalcations through the years,

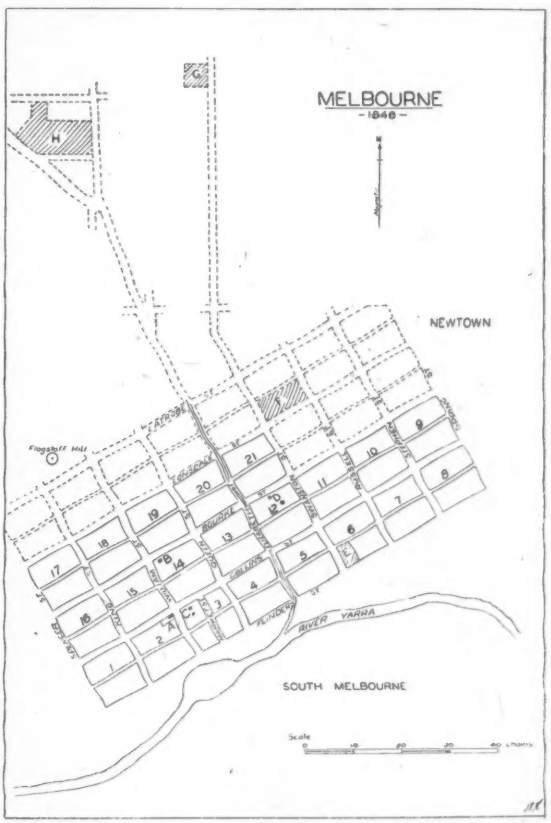

FIGURE I.

Plan of Melbourne in 1848. A = two-storey brick house built by Batman. B = house built of straw and mud by J. P. Fawkner. C = site of temporary hospital behind gaol. D = possible sites of second temporary hospital. E = Hay and Corn Market site. F = Melbourne Hospital site. G = future Medical School site. H = future Royal Melbourne Hospital site.

but absconding with the proceeds has to be conducted more subtly, and the arms of the law are longer and surer in their enfolding embrace.

It is sad but amusing to find a wail at the expense when, in 1852, "the Committee have been compelled to provide a permanent bath", but, within a couple of years, the Institute boasted a building extension which added accommodation for an additional 124 patients, a board room, apartments for the resident surgeon, a receiving room for the patients and an operating room; by then there were two bathrooms!

There is a whimsical solatium for the doctors in the seventh annual report. After mentioning that 48 less deaths

had occurred, only 276 out of 1605 in-patients having died during the year, we read:

> Whilst acknowledging, primarily, the providence of God, they cannot avoid stating their confident conviction that this result is mainly attributable to the constant care, skill and attention of the medical officers, including the Resident Surgeon, Mr. Garrard, and the improved condition of the Institution, under the really efficient management of the present house steward and matron, Mr. and Mrs. Williams. Of the exertions of these officers the Committee desire to speak in terms of the highest commendation; for, not only have they enforced strict order and cleanliness, but Mr. Williams has, in every way connected with his department, shown the most praiseworthy desire to economize the funds.

Later in the same report we discover that the doctors "now generally direct the supply of a good generous diet for the sick" and, by exerting professional pressure, had induced the Committee and its very frugal Mr. Williams "at considerable expense" to provide eggs "for those whose state of health prevented them from taking other food; while milk and vegetables, instead of being articles rarely tasted by the patients, have been regularly supplied". The water supply for all purposes came from the well alongside (and perhaps in part off the "dilapidated roof" of wooden shingles) and was pumped to the kitchen, to the "water closets" and to the two "permanent" baths. It was a precious commodity, though it had a great knack of getting out of its appointed channels. But the hospital filth and quagmires were not considered unreasonable health risks, while Elizabeth Street was a poorly disguised creek bed which had periodically to be "rendered passable" and St. Francis's Church was sinking into the morass alongside, which was called a city street. It was noted later with satisfaction that bread was baked in the hospital and that vegetables were supplied without the interposition of middlemen; illuminant gas became available and it was also used in the laundry and drying room; and "thanks to the liberality of the Water and Sewage Commission, a plentiful supply of water has been laid on by them in every ward, at an expense for piping and labor of £67 10s.".

Such were the conditions then in which the salvage work was attempted in the fifties. It was found early that the honorary medical staff was too large and it was reduced to two physicians, J. B. Motherwell and A. C. Brownless, and two surgeons, E. Barker and W. Gillbee; they had the aid of a resident house surgeon who also soon had an assistant. The first resident house surgeon was Dr. Richard Croker Graves, but the name was ill-omened, for he died in office soon afterwards and was succeeded by Dr. Garrard, the first of a long line of senior resident officers to give outstanding service to the Hospital and thereby to gain honour and fame for themselves. Each of the four named members of the visiting staff became distinguished and served the community long and faithfully, adding lustre to the profession from which they sprang. Dr. Palmer and Dr. Greeves are examples of many-sided people with medical degrees who distinguished themselves in municipal and legislative spheres and in business life, rather than in the practice of medicine.

Medical practice was crude enough in all conscience, but the practice of surgery was very restricted; operative surgery had scarcely emerged from barbarism, and it is fortunate that very few operations were attempted at the Hospital except manipulations of a minor nature. The chief causes of death were recorded as "fever", "dysentery", "phthisis" and "debility". Even nowadaye it is unavoidable that occasionally the diagnosis of "fever of uncertain origin" is recorded, but in 1856, 248 out of 1725 in-patients were thus labelled and 40 of them died in hospital—a big improvement on the results in previous years.

The Sixties.

From the professional point of view the sixties were the last years of the Dark Ages heralding the dawn ushered in by Pasteur and Lister. Dr. G. T. Howard has published an interesting sketch of the Hospital as it was in 1860 with his historical contribution to the first number of *The Melbourne Hospital Clinical Reports*. It then still faced west to Swanston Street and occupied only about one-quarter of the hospital reservation. The original grant of land had been extended considerably in 1852 with the strange condition that it should not be built upon. Dr. B. T. Zwar, in *The Melbourne Hospital Clinical Reports*, in June, 1933, has published with his historical sketch an illustration of the Hospital as it looked in 1862. It is apparent that it was substantially rebuilt and considerably enlarged between 1860 and 1862. This must be appreciated to understand the points at issue between the authorities at the Melbourne Hospital and those at the university.

The most important feature of the decade for us to discuss is the culmination in 1864 of the plans for a medical school as an integral part of the University of Melbourne and the negotiations for obtaining teachers and clinical material at the Hospital.

On June 16, 1855, Dr. Anthony Colling Brownless, Honorary Physician of the Melbourne Hospital and of the Benevolent Asylum, was gazetted a member of the University Council. He was a man of outstanding ability who had graduated in London in 1841 in his twenty-fourth year. He was destined to have a large private practice, to remain on the active staff at the Melbourne Hospital till 1868, to be chosen annually as Vice-Chancellor of the university for twenty-nine years, and to be its Chancellor for ten years afterwards till his death on December 3, 1897, covered with academic, civic and ecclesiastical distinctions of the highest order.

Dr. George Britton Halford was the first professor and gave lectures and demonstrations in anatomy, physiology and pathology commencing in 1863. By then he had planned a splendid curriculum for a medical course, the candidates to spend five years over it and to pass five annual examinations—the stiffest course then known anywhere. By 1864 three third-year students were ready for clinical tuition at the Melbourne Hospital and the fine buildings at the university were approaching completion. The living stream of lads and lasses has never ceased to flow—and never will.

This clinical teaching problem bristled with difficulties and caused much heart-burning and perplexity. The leading members of the honorary staff, previously inexperienced in clinical teaching of a formal nature, were not in the habit of being at the Hospital longer or more frequently than was necessary to discharge their duties to the patients. This additional responsibility was not to be undertaken lightly. The Committee and the doctors were somewhat distrustful of what appeared to be a formidable challenge from the University Council to interfere in matters which were till then the close preserve of the Hospital authorities. Indecision rather than opposition, procrastination rather than defiance, fanned the flames of controversy, the merits and demerits of which it is difficult to evaluate at this distance. Brownless wanted a teaching hospital in the grounds of the university, to the south of the Medical School buildings, under the control of the University Council, exerted through the Faculty of Medicine. He was supported by a strong body of medical opinion, but was opposed by the Committee of the Melbourne Hospital. The rebuilding of the Melbourne Hospital near the university was favoured as the alternative and a New Hospital Committee was formed.

On April 2, 1864, Dr. James Robertson was appointed Lecturer in Medicine and Mr. Edward Barker Lecturer in Surgery at the Medical School. Dr. Richard Tracy, one of the founders of the Women's Hospital, was Lecturer in Obstetrics and Gynæcology. A year later Dr. James Edward Neild was appointed Lecturer in Forensic Medicine, a fifth-year subject. In 1866 Dr. James Bridgeham Motherwell filled the death vacancy of Mr. Haines, the Honourable the Treasurer of the Colony, on the Council. The Melbourne Hospital staff was thus strongly represented in the leadership on medical affairs at the university.

Dr. James Edward Neild and Dr. Palmer were such remarkable men that a digression about them will not be out of place in this narrative. Born in Yorkshire in 1824, Dr. Neild came to Victoria in 1853 and engaged in journalism of all descriptions, in addition to occupying the lectureship in forensic medicine for forty years. He was one of the best known musical and theatrical critics in Australia. Dr. Neild was also prominently associated with the Medical Society of Victoria and was the editor of the *Australian Medical Journal* from 1862 to 1879. In 1880 he was very active in the formation of the Victorian Branch of the British Medical Association. He was a cultured, energetic, able, amiable and interesting man, whose opinion carried great weight in the community.

In 1857 Dr. Palmer became the Honourable Sir James Frederick Palmer, shortly after promotion from Speaker to President of the Legislative Council of Victoria. He continued to be President until his retirement in 1870. For many years he was also Chairman and President of the Melbourne Hospital. He was by no means popular, being forceful and aggressive, though silver-tongued. He fought like a tiger to get his own way and would not brook opposition. Unfortunately he made some bad errors of judgement. In the business world he was well known as a prosperous wine and spirit merchant and there was a very large demand for his wares.

The New Hospital Committee had a stormy passage and almost failed to achieve its purpose. After a while the Melbourne Hospital Committee admitted that there really

was need for additional accommodation, at least for those with long-term illnesses; if the Melbourne Hospital was to be a teaching hospital it would be well to have a more rapid turnover of beds. Just at that time the attempted assassination of His Royal Highness Prince Alfred, Duke of Edinburgh, in Sydney had created a move there for the establishment of a general hospital—now the Royal Prince Alfred Hospital—as a thanksgiving memorial. The precedent was grasped in Victoria and the activities of the New Hospital Committee resulted in the establishment of the Alfred Hospital in Prahran, on 25 acres of park land, between St. Kilda Road and Punt Road. It was suitable as a general hospital for the residents south of the Yarra, but a stipulation was made that it, too, was to be recognized by the university as a teaching hospital, complicating the original problem considerably. Prince Alfred laid the foundation stone on March 6, 1869, and the hospital was opened in 1870.

In 1914, in connexion with the Jubilee of the Medical School, Mr. G. A. Syme stated that, in 1863, there were eight honorary physicians and eight honorary surgeons at the Melbourne Hospital who all attended out-patients as well as in-patients. He went on to say that, in 1872, four of the physicians restricted their attention to in-patients and four assistant physicians took charge of the out-patients and that similarly, in 1875, four surgeons and four assistant surgeons divided the work.

The Seventies.

In medical politics the feature of the seventies was the extraordinary rumpus over the respective functions of Medical School and Hospital in the clinical instruction of medical students. Editorial comment is made on this matter in *The Australian Medical Gazette* of March, 1871, drawing attention to the "unaccountable neglect of the university to provide clinical lectures for its students in medicine". The late B. T. Zwar has given an excellent *résumé*, published in *The Melbourne Hospital Clinical Reports*, of the way in which the atempt to foist the responsibility for formal lectures on to the Committee of Management was countered, until in 1884 Dr. John Williams was appointed Lecturer in Clinical Medicine and Mr. Thomas Fitzgerald Lecturer in Clinical Surgery, and in 1886 Dr. Fulton in medicine and Mr. Girdlestone in surgery joined them. When the new curriculum came into force in 1888, the medical staffs of the clinical schools officially accepted the responsibility for making all arrangements for providing clinical instruction.

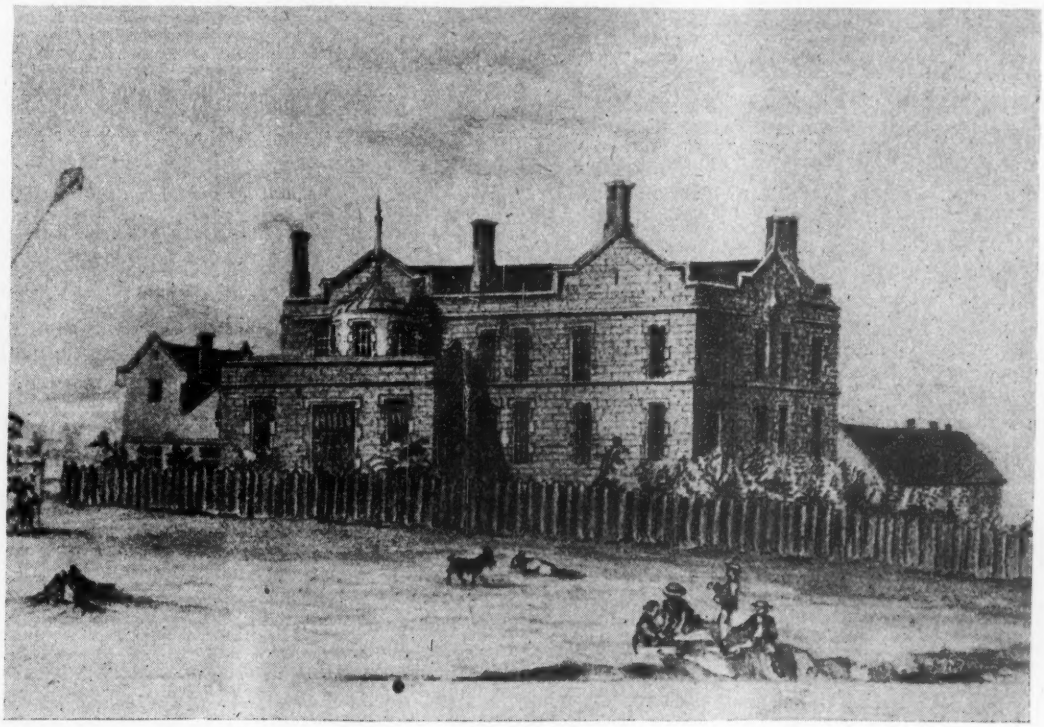

FIGURE II.
The first Melbourne Hospital, opened March 15, 1848.

In the *Australian Medical Journal* of April, 1868, there is an editorial article, doubtless by Dr. Neild. In it he states that the Medical School had not received cordial support from the profession; that the medical staff of the Melbourne Hospital had not shown a desire to facilitate the clinical studies of the students; and that the Council of the university had refused permission for a hospital to be built on vacant ground near the Medical School. Nevertheless a hospital should be "erected in the north-west quarter of the city" and "the selection of any site other than one near the Medical School would fail to fulfil all the purposes that are to be accomplished in its establishment. The apathy and antagonism of the profession, added to the determination of the lay advocates of another site, may prevent for a time the proper consummation being achieved, but that sooner or later it will be achieved, we are firm in the belief". This prophecy of Dr. Neild was fulfilled on December 11, 1944, when the Royal Melbourne Hospital was transferred to its magnificent new home at Parkville. With the establishment of the Alfred Hospital the first of what was known as the Battles of the Sites ended in the discomfiture of the advocates of the vision splendid—it died away and faded into the light of common day.

Antiseptic surgery was introduced into the work at the Melbourne Hospital remarkably quickly after Lister had applied Pasteur's germ theory and announced his technique in 1867. A young surgeon—Dr. Newmarch—temporarily in Melbourne—had just been house surgeon to Lister and carbolized dressings and carbolic spray apparatus were in use in Melbourne ten years before the novel ideas made any considerable headway even in the big London hospitals. Sir James Barrett has recorded the relevant facts for us in his recollections of his student days, published in *Royal*

Melbourne Hospital Clinical Records and again in "Eighty Eventful Years". Sir James William Barrett and Sir George Adlington Syme both graduated in 1882. Earlier graduates of Melbourne included Sir Harry Brookes Allen and William Snowball in 1876, Robert Stirling in 1878, Peter Bennie in 1879, John William Springthorpe in 1880, and Felix Henry Meyer in 1881. They were soon joined by Frederick Dougan Bird and William Moore in 1883, Crawford Henry Mollison in 1885, and many other famous colleagues as the school grew larger. All of these men exerted a profound influence on medical thought and practice in Melbourne, and many of them at the Melbourne Hospital itself. The application in medicine and surgery of the conception of immunity, elaborated from the ideas put forward and proved by Louis Pasteur, revolutionized preexistent routine and ushered in a new era for doctors and their patients.

In looking over the pages of the *Australian Medical Journal* and *The Australian Medical Gazette* in the sixties and seventies we can get an impression of the things that really mattered in the pre-Listerian days. The effect is chastening, for to a modern person most of the debates are stupid and many of the notions puerile; one cannot escape the pessimistic reflection that within a generation or two our shibboleths also will be shattered. The tussle seemed to be between the fierce passion for phlebotomy, even to the point of bleeding till syncope was reached, which was becoming an obsolete obsession in the seventies, and the new craze for replacing this "depressant" treatment by "stimulation" with the galvanic battery, mesmerism or such alcoholic medicaments as porter, wine and strong spirits. The stimulators held sway and the brandy, wine and porter flowed in the wards. The depressors still kept the lancet at work, but were usually content with five or six ounces of blood at a time. There was also a swing away from drug therapy to homœopathy and ineffective posology emerged as a compromise, which diminished the usefulness of the physicians for many a long day thereafter; indeed its effects are still with us, especially in the pages of the official British Pharmacopœia.

Thomas Naghten Fitzgerald was the central figure in one of the occasional unpleasant brushes between the members of the Committee and the honorary staff. In somewhat humiliating circumstances he was asked to explain why he ordered so much porter for his patients. His defence was that in his opinion it supported them through his surgical treatment, and that though hitherto he had supplied most of it privately, he considered that it was up to the Committee to pay for it. This defence was regarded as contumacious, but Fitzgerald emerged scathless from the encounter when, on calling for a report on the use of alcoholic stimulants, the Committee established to everyone's satisfaction that Fitzgerald was among the least extravagant members of the staff in this respect.

Another *cause célèbre* was the charge of malpraxis brought against Mr. Edward Barker for the loss of a leg, alleged to have been the outcome of his use of a ring splint for fracture of the patella. The verdict was for the plaintiff and Barker was fined £300. His colleagues had a spirited indignation meeting and soon subscribed the amount of the fine between them. It was established, however, that each member of the staff was responsible for his professional actions and that the Committee was not liable for damages.

Another anecdote of those times illustrates friction between the resident medical staff and the Committee. The rules of the Hospital were ridiculously stringent and the resident surgeon, his assistant and matron were expected to supply continuous service and never to absent themselves for longer than three hours on any occasion. In the incident under review the Committee pressed the resident surgeon to give his reasons for absence from the premises and claimed the right to know where he went and what he did when not on duty. The Committee lost again and the offensive rule became a dead letter.

The Eighties.

In the eighties one of the highlights was the revision of the curriculum of the medical course in 1887, coupled with the consummate capacity of the future Sir Harry Allen, who took over the multifarious responsibilities of the aging Professor Halford. In 1882, though only twenty-eight years of age, Allen became professor of anatomy and pathology and held the double chair till R. J. A. Berry relieved him of the anatomy department. From 1906 till his retirement from the professorship of pathology in 1924, Allen was the doyen of the Medical School. His influence on the work at the Melbourne Hospital was very great, for he attended daily for many years to do the autopsies and to expose the truth by relating the findings to the bedside facts and fancies, to the great intellectual benefit of the honoraries and the medical students.

In 1882 erysipelas was prevalent in Melbourne and there was a public outcry when it became known that deaths were occurring in Melbourne Hospital because of cross-infection.

The Committee appointed an important Subcommittee of Inquiry. A return of the number of deaths from erysipelas in the Melbourne Hospital is among the "Parliamentary Papers of the Legislative Assembly" (C13, 1882/83). Overcrowding of patients was shown to be one of the causes of the cross-infection. Seventy beds were withdrawn from the 389 which were then being occupied and many other minor improvements were effected. It is of importance to record that this inquiry exposed the imperfect adoption and misapplication of Listerian principles. The Coroner of the day was frequently caustic in his comments, which also had a salutary effect in bringing about radical improvements. A new era opened for relief by surgery and there was soon a fine tradition established. Since those days the Hospital has never lacked surgeons of outstanding brilliance and there have usually been some at work in the operating theatres who have reached the highest eminence attainable anywhere, some of whom are happily still with us.

As may be readily surmised, this exposure of the unsatisfactory state of the Melbourne Hospital—and by inference of the other public hospitals—resurrected from the smouldering ashes the phœnix of the model teaching hospital near the university. It was not long before another "Battle of the Sites" commenced, but the forces for and against moving from Lonsdale Street were closely engaged in wordy warfare for many years.

An excellent editorial article appeared in the *Australian Medical Journal* on March 15, 1889. As it is very informative and full of facts relevant to the period, I cannot do better than to quote it *in extenso*:

> There are certain subjects which arouse public attention for a time, almost at periodic intervals. They seem to lie dormant a while, and gradually gather force, until attention is again attracted to them. Then letters are written to the papers, followed by leading articles, indignation is expressed, and then things once more settle down to the old routine. Such is the case with the condition of the Melbourne Hospital. For years complaints of its inadequacy have been periodically made, and yet it remains pretty much as it was. No one appears to deny that the present buildings do not supply sufficient accommodation, or that they are not exactly a model of hospital construction, but nothing is done to improve matters. Complaints made to the General Committee are referred to the Building Committee, and there is an end of them—they are quietly shelved.
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> It may not be uninteresting to compare the hospital accommodation of Melbourne with that of large towns in Great Britain. We are informed that the Melbourne Hospital has 299 beds, the Alfred Hospital 144, the Homœopathic 60, the Children's Hospital 70, the Infirmary Department of the Women's Hospital 25, giving a total of 598 beds to a population of 390,000, or one bed to every 652 of the population. We find that in Dublin the accommodation is one bed to every 140 of the population, Belfast has one to 380, Edinburgh one to 410, London one to 420, Birmingham one to 700, Sheffield one to 830. Thus Melbourne, while far behind the capital cities of England, Scotland and Ireland in the matter of hospital accommodation, is ahead of leading English provincial towns. It must be remembered, however, that these figures do not include the beds in the poor-law infirmaries, which take in a large number of serious and urgent cases in Great Britain.
>
> The most conclusive evidence of the insufficiency of hospital accommodation in Melbourne is the fact that serious cases have daily to be refused admission for want of room. The Superintendent of the Melbourne Hospital informs us that, from February 25 to March 12, 52 patients were refused admission for want of room; and the Resident at the Children's Hospital states that it is also overcrowded, and that 15 cases of typhoid fever were refused last week. The Alfred Hospital has for the past three seasons provided beds in tents for 20 to 30 patients.
>
> It would be very easy to say some hard things about such a condition of affairs, but we refrain. Surely the simple facts speak with sufficient eloquence. Fifty-two patients deserving admission turned away from the doors of the Hospital in a fortnight, simply from want of room! But this is not the worst evil. The mortality returns of the Melbourne Hospital are exceptionally

high; nearly 17 per cent. of the cases treated die. In England and Wales the percentage is only about 11; and in the German Empire only 7. The explanation probably is, that patients cannot gain admission to the Melbourne Hospital until their condition is so exceedingly urgent that many of them are then past help, who, had they been admitted earlier, might have recovered.

The present state of affairs is simply a disgrace to the community, and we can only repeat what has always been urged in this journal, that the Melbourne Hospital must be rebuilt on another site, and that the best site that could be obtained would be that now occupied by the Corporation Horse and Pig Market. We are confident that when the public are made fully cognisant of the urgent necessity, the funds will be forthcoming; in fact, nearly all that would be needed would be obtained by the sale of the present site. Surely the City Council will not obstinately stand in the way of the removal of a scandal of such magnitude.

In 1880 Victoria was sufficiently prosperous to stage a great International Exhibition in a magnificent building costing one-quarter of a million pounds, especially built in the Carlton Gardens, from then onwards to be known as the Exhibition Building and Gardens. This utilization of a fine site had disqualified it as a possible position for a hospital, but it had demonstrated that Victoria had grown to be an independent country of commercial and cultural interest to the other nations. The Centennial Exhibition of 1888 provided the occasion on which this progress could be demonstrated, for nearly one hundred countries sent between them over one thousand fine exhibits. A land "boom" of great magnitude occurred. Many-storeyed new buildings and great blocks of offices appeared and public monuments were erected. The town hall got a fine portico, the post office a third storey. The Houses of Parliament were resurrected from architectural obscurity by the construction of the sweeping line of stone steps at the east end of Bourke Street. Many other handsome governmental and municipal buildings appeared. The Melbourne Hospital was substantially repaired and extended, standing surrounded by beautifully kept gardens in Lonsdale Street. Shabby remnants of the old buildings remained, such as the awful old out-patient department at the back, along Little Lonsdale Street to the Russell Street corner.

History repeated itself when, in 1893, Saint Vincent's Hospital was founded in Victoria Street to become a third clinical school and closer to the university than either of the others. During this "boom" period the fantastic over-organization of welfare services reached such a pitch that charity had to be sold skilfully by devious commercial methods. The widespread prosperity reduced the number of claimants for charitable relief, but at no time was the public hospital bed position in the city unquestionably satisfactory.

The Nineties.

The "boom" broke rather suddenly and a terrible "depression" followed. In August, 1891, four banks closed, and within the next year the operations of twenty-one trusted financial bodies were suspended, holding up payment to depositors of £11,000,000 and calling up £4,600,000 of unpaid capital. Two good seasons with abundant harvests and increased gold output were insufficient to prevent bankruptcies and widespread unemployment which reached a peak in 1894. Strengthening of membership of trade unions, medical clubs and friendly societies helped to spread the risks for the lower income earner, but introduced a new large group of persons, intermediate in classification between the self-supporting class and the destitute. This lower income group has progressively swelled the clientele of the public hospitals and provision has had to be made for it in planning extensions. There has also been a constant trend upwards in the income to be designated as "low", but for many years the Hospital authorities succeeded in preventing serious imposition. The impingement on hospital and medical policy of club practice and medical benefits in "workers'" organizations has been well ventilated in medical literature and progressive concessions have been made indicative of generosity and liberality to the under-privileged groups.

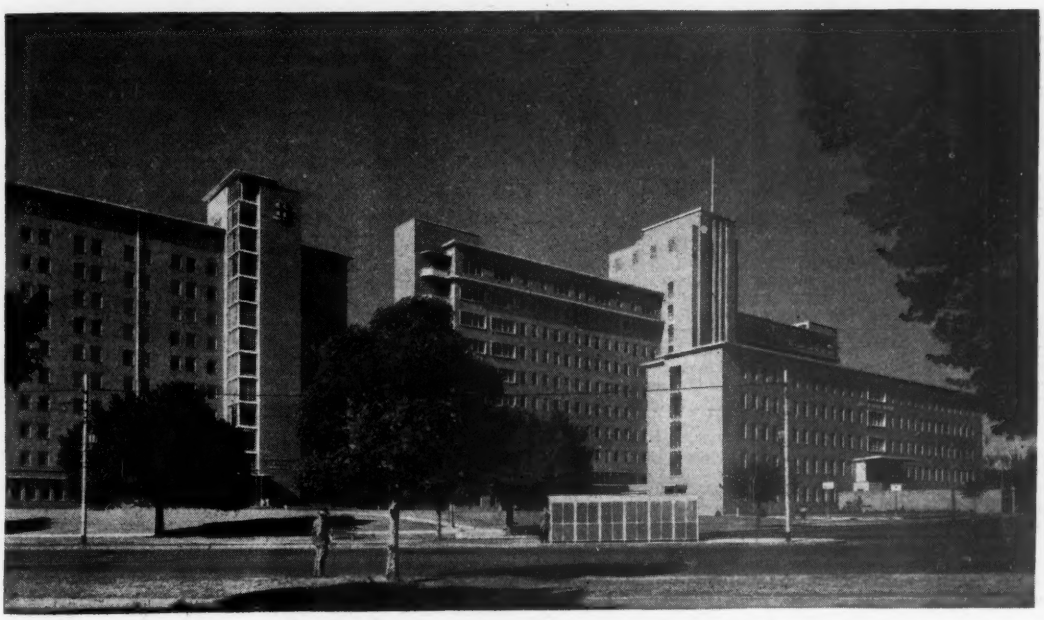

FIGURE III.
The Royal Melbourne Hospital at the present day.

At the Melbourne Hospital the nineties were the years when giant actors strode the boards. The great Fitzgerald dominated the stage, winning his way to the leadership of the profession in Australia and to the proud position of Consulting Surgeon to the British forces in the field during the Boer War. Like many great surgeons to follow him at the Melbourne Hospital, he was not eloquent, but taught and inspired others by his example and his extraordinary acquisition of the immortal flair—the *tactus eruditus* and the surgical judgement *in excelsis*.

William Moore, our first local Master of Surgery (1885), G. A. Syme, Fred Bird and Robert Stirling were among those who followed in the footsteps of the great Fitzgerald and earned their individual laurels. As they aged in the early years of the present century they developed an aura which is difficult to define. Stirling and Syme were wisdom

personified, but were not loquacious. Bird exuded bonhomie and courtliness. The loud guffaws and bluff heartiness of Charles Ryan caused resounding echoes through the hospital wards and corridors. Aseptic surgery was replacing the older antiseptic practices slowly but surely, though yet another generation had to come before the High Priests of Sacred Cleanliness hauled down the flag of Sepsis—the Arch-Enemy of Surgery.

On the medical side the great John Williams was the towering figure. He is justly regarded as the teacher *par excellence* who made clinical instruction a reality at the Hospital. He is the prototype of the systematic clinicians who have taught students, of undergraduate and post-graduate classes, so faithfully, efficiently and successfully that no longer could the absence of academic qualifications as "educationists" be a slur on the clinical teachers. John Williams served the Hospital nobly from 1875, when he was appointed resident medical officer, till 1904, when he resigned his appointment as physician.

Professor Baldwin Spencer, Professor David Masson and Professor C. J. Martin were sending well-trained scientists along as medical students to the Hospital to have the superstructures placed on sound foundations.

In 1892 Grace Clara Stone and Margaret Whyte graduated as the first of a never-ending stream of female doctors prepared to see and to do whatever was required of men in a professional respect.

During the nineties not only were the members of the honorary staff graded as physicians and surgeons, but further specialization became desirable and this division of labour has become a feature of twentieth century practice. New departments for specialists have been added in great profusion. Whereas in the early days the whole field of medical work could be cultivated adequately by any one man, progressive complexity of detailed knowledge has made that ambition impossible, as the standards of a great teaching hospital are very exacting.

One important new undertaking was the serious professional training of nursing sisters. After preliminary planning, Miss Isabella Rathie was appointed Lady Superintendent in 1890 and the new training school for nurses was set up under her direction. The training period originally was only two years, but, after eight years, it was extended to three years. From 1895 to 1901 Miss Martha Farquharson capably conducted the training which has been an outstanding feature of the work of the Hospital ever since.

Even at this stage of the life of the Melbourne Hospital we note that teaching and training had been added to the original function of healing to so notable an extent that locally trained doctors, nurses and other scientific workers were going away from Melbourne to important positions elsewhere, spreading the influence of the parent hospital far and wide. This migration has increased as the years have passed and has helped considerably to enhance the Hospital's prestige and reputation.

The Century of Miracles.

On entering the twentieth century, the population of Melbourne passed the half-million mark. The people were prosperous and optimistic, eagerly looking forward to the long-awaited Federation of States, henceforward to be known as the Commonwealth of Australia, ceremonially established just before the death of Queen Victoria.

The horse and buggy days for the doctor rapidly disappeared as motor-cars became efficient. In the early years of the century electricity and telephones facilitated his work. Soon an amazing eddy in time swept all before it, making the vivid imagination of a Jules Verne seem humdrum in the extreme. The inventive genius of man has never been more productive than in the first half of the twentieth century. Changes in transport, communications and production have improved the standard of living, but new dangers and difficulties have replaced the older troubles. Twice the nations of the world have been for several years locked in warfare of the fiercest kind, unable otherwise to adapt themselves to the rapidly changing environment. Many of the most important medical posts have been held by Melbourne Hospital personnel during these great world wars and the service record on each occasion is a distinguished one. The Royal Australasian Colleges of Surgeons and Physicians owe an enormous debt for their origins to the members of the staff of the Melbourne Hospital. The Hospital became "Royal" itself in 1935.

Melbourne's population has reached 1,200,000 persons, living in a highly urbanized state, sprawled out over a large area so that the periphery is far from the centre. Social welfare workers have been required in ever larger numbers, and it has become essential that they should acquire highly specialized knowledge where they can get great practical experience. The effect on organizations such as that of the Melbourne Hospital has been the provision of courses of training not only in doctoring and nursing, but in all the ancillary medical occupations, including massage, physiotherapy, hospital almonry, dietetics, cooking and laboratory and scientific work of all descriptions. The Melbourne Hospital Committee has been foremost in supplying all these requirements, employing highly trained staff to do the special work and also to conduct the courses of instruction.

In the years before the rebuilding of the Hospital on the Lonsdale Street site, just before the first great world war, an important phase of the "Battle of the Sites" took place. William Moore was the leader after Fitzgerald and Williams had had their day. He soon had enthusiastic helpers, such as David Grant, William Boyd, Henry Maudsley, Richard Stawell and later Bernard Zwar and others, many of whom it is invidious to name as the history approaches its culmination. The Roll of Honour was published by Zwar quite recently when he was President of the Hospital and the victory had been won.

In 1908 the decision to rebuild on the old site was made because of the terms of the magnificent gift of £135,000 to the Building Fund from the Edward Wilson Trust. After six months of feverish effort to secure a site at Parkville had failed, it was necessary to rebuild on the old site, in order to claim and utilize the Edward Wilson Trust donation.

The members of the honorary staff and committee who were firmly in favour of the Parkville site never ceased to keep the matter well in the foreground, and as soon as the expanding demands demonstrated the lack of flexibility even of the newly built hospital, the agitation was revived. Sir Stanley Argyle, who had been a member of the honorary staff of the Alfred Hospital, had attained eminence in the Legislative Assembly. He was very helpful in assisting to form governmental opinion in favour of the transfer to the Pig Market site at Parkville. A Government Commission travelled abroad and reported on the paramount advantages of proximity of teaching hospital and medical school. Legislation was drafted to make the scheme practicable. Argyle even became Premier of the State, to be defeated at a critical stage for the Melbourne Hospital. Disappointment followed on disappointment, until at last the political stage was held sufficiently long by the Honourable A. A. Dunstan, as Premier and Treasurer, for final decisive action. An Order-in-Council, gazetted on July 3, 1929, permanently reserved a little over ten acres of the Market Site at Parkville for the purposes of the Melbourne General Hospital. Four weeks later the final proclamation was made in the official *Gazette*. Sir Stanley Argyle was then Chief Secretary and Minister of Health. After another attempt to get the Committee to extend the Hospital with new buildings on the cramped old site had been refused by the Committee, a period of inaction followed. At last, in May, 1935, agreement for financial assistance was reached in conference, under the leadership of Mr. Dunstan, the Premier, provided that the Government purchased the old site and that the Hospital made available, on the site at Parkville, room for the erection of certain medical school departments of the university and also safeguarded the interests of the clinical schools of the Alfred and Saint Vincent's Hospitals. At an earlier stage, in February, 1933, another condition was imposed for "the early provision of accommodation for intermediate and private patients".

The building contracts were signed on November 22, 1938. Mr. Dunstan, then still Premier of Victoria, at a ceremony, commenced the preliminary excavation work. Building operations proper started on January 8, 1940, and the main building work was completed on December 10, 1943. The cost was approximately £1,100,000.

Fortunately the wonderful Palace of Healing was ready for occupation when it was eagerly sought for use by the Fourth American General Hospital "staffed by members of the Lakeside Hospital of the Western Reserve University, Cleveland, Ohio, U.S.A.". Zwar goes on to inform us that "it was handed back on March 31, 1944. During its occupancy by the Fourth American General Hospital more than 42,000 sick and wounded American soldiers received nursing and medical attention within its buildings".

A canard went the rounds that the Americans had paid handsomely for the use of the Hospital and thus eased the financial position for the Committee. This has been authoritatively denied. The Committee merely resumed control of the buildings in a good state of repair—the financial transaction was entirely one between the governments concerned.

I have reserved for final consideration the fascinating feature of the century—the enormous extension of clinical and laboratory investigational and research work. Great

departments have sprung up, which broaden and deepen the scientific background.

Right from the introduction of radiology, the Melbourne Hospital Committee has made provision for its utilization in the work of the physicians and surgeons. Expensive apparatus has had to be installed and scrapped time after time as improvements have become available. The expert staff has been housed suitably and has grown larger and larger numerically. Radiotherapy has required similar provision. Biochemistry and hæmatology are other examples.

Clinical research of the highest quality has been conducted brilliantly and its future is assured. The application of the work done and to be done by the new Clinical Research Unit is of incalculable value. The Walter and Eliza Hall Institute of Medical Research, though separately incorporated, has from its foundation been closely associated with the Melbourne Hospital and it now occupies handsome new quarters at Parkville with the Royal Melbourne Hospital.

The Red Cross Blood Transfusion Service has one floor of the main building, and, as a result of the war, has become an important service for civilian requirements.

Provision has been required for housing over thirty resident medical officers and four hundred nurses.

A full description is available elsewhere of this "Palace of Healing" which is a city within a city, full of people who are busy in a variety of occupations which is almost as diversified as that of the population of any other city.

Eleven hundred thousand pounds of capital are represented—480 patients with acute illness are in the wards. The building is not finished. Six more wards await construction to house 150 more patients. The Centenary Appeal is for one hundred thousand pounds to build and equip these additional wards. Even as a business proposition the people of Victoria must make this further investment, and regard it as a very small gesture which the corporate conscience cannot possibly neglect.

In sketchy fashion I have attempted to depict the long vista of the years. If it is not too fanciful to suggest that a city has a soul, Melbourne's soul seems to be embodied in the Royal Melbourne Hospital. The spiritual life of the community is not experienced only in churches and cathedrals, nor are architectural gems the only lasting tributes or records of that spiritual life that are passed on to posterity. The speaking dust of its great ones, the noble traditions of industry and of triumph over difficulties, the loving labours and the great sacrifices have been handed on to us. We have a goodly heritage and are but temporary stewards, each contributing if possible a little to that "spirit of the place" which acts as a driving force, an encouragement and an inspiration to those of each succeeding generation.

Political ideas of social security for all are being formulated and great scientific advances are being made. We are justified in believing that we are not only participating in the funeral ceremonies of a century at the Melbourne Hospital, but are also privileged to be witnesses of the dawn of a blazingly glorious new one. With the utmost confidence, taking courage from the achievements of the past, we can predict that our sons and their sons will carry the torch on unsullied, keeping the immortal flame always burning brightly.

H. BOYD GRAHAM.

Medical Societies.

THE PUBLIC MEDICAL OFFICERS' ASSOCIATION OF NEW SOUTH WALES.

THE twenty-second annual general meeting of the Public Medical Officers' Association of New South Wales was held at British Medical Association House, 135, Macquarie Street, Sydney, on January 22, 1948, DR. GRACE CUTHBERT, the President, in the chair. Twenty-two members were present.

Minutes.

The minutes of the previous annual general meeting and of the special general meeting were read and confirmed.

Annual Report.

The annual report for 1947 was explained by the Honorary Secretary and adopted. The report is as follows.

The unsettled social and economic state of the nation continues to render increasingly difficult the conditions under which most public medical officers have carried out their duties during 1947. It has also made more difficult the task of the committee in seeking to improve the working conditions of members.

The membership role of the Association now contains 121 names, including 11 honorary members. It is regretted that it is necessary to record the death of Dr. C. Henry (Mental Hospitals Group).

During 1947 the committee met nine times, attendance of members being as follows: Dr. G. Cuthbert (President), 9; Dr. E. T. Hilliard, 5; Dr. W. Audley, 1; Dr. G. B. Wooster, 1; Dr. E. Wallace, 8; Dr. J. McManamey, 9; Dr. G. C. Smith, 3; Dr. E. Meyers, 5; Dr. C. England, 7; Dr. D. McClemens, 2; Dr. J. Rossell, 6; Dr. W. Flook, 7; Dr. G. Saxby, 4; Dr. A. Edwards (Secretary), 9.

Dr. Audley and Dr. Wooster were elected Group Representatives as from October 13, 1947, *vice* Dr. H. H. Nowland and Dr. S. E. Jones. Dr. Meyers was elected Group Representative *vice* Dr. Smith on May 13, 1947. Dr. E. Wallace was elected Treasurer *vice* Dr. G. C. Smith on May 13, 1947.

Representations were made to the Public Service Board in reference to the following matters.

1. It was sought to have rates of pay for female medical officers raised to an equality with that of male officers doing similar work. The Board refused to accede to this request, but will reconsider the matter when the present salary agreement is due for renewal.

2. The attention of the Board was drawn to the inadequate office accommodation provided for medical officers at 52, Bridge Street, and 93, Macquarie Street. The Board undertook to keep these representations in mind when allotting office space if and when it became available.

3. The long-standing grievance of the inadequacy of the so-called privilege leave for officers resident in institutions has at last been rectified by the Board's granting 100% increase in privilege leave, namely, two days weekly in lieu of the previous one day.

4. The unsatisfactory conditions of many residences in institutions was brought to the notice of the Board, which has undertaken to carry out the necessary work as and when conditions of labour and materials permit.

5. The necessity for the filling of vacant positions and the temporary filling of the higher positions where medical officers concerned are absent on extended leave has been the subject of a recent communication. No reply has been received as yet.

A special general meeting held on September 30, 1947, to consider the question of the registration of the Association as a union decided against such action provided that the results of future negotiations with the Public Service Board regarding salaries and conditions are satisfactory.

It is a matter for regret that, though the replies of the Board to matters raised during the year have in general been cooperative, existing conditions have prevented any further practical results.

A. T. EDWARDS,
Honorary Secretary.

Financial Statement.

The Honorary Treasurer presented the financial statement for 1947, which was adopted.

Election of Office-Bearers.

The following office-bearers were elected for 1948:

President: Dr. E. T. Hilliard.

Honorary Secretary: Dr. A. T. Edwards.

Honorary Auditor: Dr. J. McGeorge.

Committee: Dr. J. McManamey, Dr. C. W. England, Dr. E. S. A. Meyers and Dr. E. Wallace (Health Department), Dr. D. McClemens and Dr. W. K. Flook (Education Department), Dr. U. Brown (Works and Railways), Dr. G. C. Saxby (Repatriation), Dr. G. B. R. Wooster and Dr. Sands (Mental Hospitals).

Two further representatives of the mental hospitals group are to be elected by that group.

Other Business.

A motion that the meeting endorse the committee's interpretation of Rule 3 in reference to eligibility for membership—that is, that medical men employed by public bodies on a fee-for-session basis be eligible—was carried.

A motion that the committee should explore the question of insurance of members as a group and/or as individuals against the results of legal actions was carried.

Special Correspondence.

LONDON LETTER.

FROM OUR SPECIAL REPRESENTATIVE.

"The Fight is On."

THIS phrase might well be taken as the signature tune of the Special Representative Meeting of the British Medical Association held in London on January 8 to consider the form and implications of the plebiscite to be held in the first fortnight in February. Previous milestones have been: (i) Discussions between a medical negotiating committee and three successive Ministers of Health, Mr. Aneurin Bevin being the present one, as to the form and scope of a comprehensive medical service. (ii) The placing on the Statute Book in late 1946 of the *National Health Service Act*, many clauses of which are at variance with present medical practice. (iii) A plebiscite of the whole profession in November, 1946, in which a majority vote, particularly among general practitioners, was cast against continuing negotiations on the rules and regulations necessary to make the act workable, on the grounds that the act violated a number of vital principles. (iv) The intervention of the Presidents of the three Royal Colleges, as a result of which negotiations were resumed on a comprehensive basis and on the understanding, given by the Minister, that amending legislation was not excluded (February, 1947). (v) The recent publication of (*a*) the profession's case as presented by the Negotiating Committee and (*b*) the Minister's reply thereto. The net result is that there is to be no amending legislation, and the act stands as it did twelve months ago, except for a minor and hypothetical concession regarding hospital beds to consultants "when circumstances permit". The act will become operative on July 5, and already a number of committees have been constituted and are at work making the necessary arrangements. The avowed policy of the Government is a full-time salaried State medical service, with certain pensionable rights, controlled by the Minister of Health, and most doctors see the genesis of such a service in the present act. It is an open secret that discussions with the present Minister have been negotiations in name only, Mr. Bevan's attitude appearing to be: "I am open to conviction, but I would like to see the man who can convince me." The main points in the act to which doctors object may be summarized as follows: (*a*) payment partly by basic salary and partly by capitation fee, the relative proportions to be settled by the Minister; (*b*) negative direction of unplaced and new doctors as to where they should practise; (*c*) denial of right of appeal to the courts in case of dismissal from the service; (*d*) abolition of the buying and selling of practices; (*e*) uncertainty as the conditions governing present partnerships after July 5, 1947; (*f*) lists to be drawn up by a committee setting out which practitioners are entitled to do midwifery. It is to be noted that (*a*), (*b*) and (*c*) above are not in the bill now being considered by the North of Ireland Parliament and that the procedure regarding midwifery does not appear in the Scottish act.

This Special Representative Meeting was called therefore to decide on the form of plebiscite to be sent out to some 70,000 doctors of whom 57,000 are members of the British Medical Association. The questions asked can be stated shortly as follows: (i) Do you or do you not approve of the act in its present form? (ii) Are you or are you not in favour of accepting service under the act in its present form? (iii) Do you or do you not agree to abide by the decision of the majority and undertake not to enter the service (*a*) if there is an aggregate majority of specialists, consultants and general practitioners against giving service, (*b*) if such majority contains not less than 13,000 general practitioners, and (*c*) if so advised by the British Medical Association. Every practitioner is asked to vote. Voting will be secret and no names will be divulged and each voter will be asked to state (*a*) how long he has been qualified, and (*b*) to which one of the nineteen groups into which the profession is divided he belongs. Such groups include specialists and/or consultants of various types; general practitioners, principals or assistants; workers in voluntary or local authority hospitals, general or special; public health or government services; teachers; research workers; the services *et cetera*.

All voters are asked to answer question (i), and in addition all general practitioners, consultants and specialists, whether holding whole-time salaried posts or not, and doctors holding whole-time positions in voluntary hospitals are asked to answer questions (ii) and (iii). The conditions set out above under which men would be asked not to enter the service require some amplification. It is obvious that there must be an aggregate majority of consultants and general practitioners against accepting service. More important still is the attitude of the general practitioners, of whom it is estimated there will be 20,000 to 21,000 available by July. It is further thought that the service cannot be run on less than 8000 general practitioners, and conversely if not less than 13,000 general practitioners refuse to take part, the service cannot function. The first two conditions of "no service" require therefore an aggregate majority of consultants and general practitioners, with not less than 13,000 general practitioners in such majority. If these two essentials are obtained the British Medical Association Council will consider the whole position at a meeting on February 18 and make a recommendation to a Special Representative Meeting to be held on February 28 where the final decision as to service or no service under the act in its present form will be taken. If the decision is no service, doctors will continue to do their work after July 5 as usual—there will not be a strike. If service is decided on, those who undertook at the plebiscite not to enter the service will be released from such undertaking.

Such is the programme of past events and some forecasts as to the future. What about the present? The Representative Meeting was business-like and rather grim. The Chairman of Council and other leaders were given an extra warm welcome and listened to more intently than usual. Long speeches were not welcome and there was an intolerance of irrelevancies and side issues; members showed plainly that their minds were made up, that they knew what they wanted, and were ready and anxious to get ahead with the work in hand. The general feeling of the meeting was crystallized in the following resolution put forward by the Bromley Division, and which, in the words of the *British Medical Journal*, "was carried immediately and without discussion, and no hand was raised against it".

> The elected representatives of the medical profession in Great Britain and Northern Ireland meeting in London this eighth day of January, 1948, solemnly declare that in their considered opinion the National Health Service Act, 1946, in its present form is so grossly at variance with the essential principles of our profession that it should be rejected absolutely by all practitioners.

There was no doubting the feelings and opinions of the representatives, but what of the doctors they represent? Do these hold the same views? The Representative Meeting in July, 1946, acclaimed the "essential principles" of the Bromley motion by votes of 241 to 12, 229 to 13, 209 to 8 and so on, but the plebiscite shortly after failed to confirm this. It is felt that circumstances are so different now that the coming plebiscite will approximate more closely to the opinions expressed at the recent Representative Meeting. In 1946 very little was known of the detailed method of working the act and many men wished to see the whole picture before giving a final opinion. Today every general practitioner can see how the act will affect him individually and the outlook is not inviting. The full terms of service for consultants are not yet available, but enough is known to make Lord Horder write in a daily paper, "once in the net, even the honorary member of a hospital staff will not escape being a civil servant". Meetings of doctors up and down the land show a general unanimity against the act ranging from 280 to 5 in the Marylebone division of the British Medical Association to 7 against, none for, and one did not vote in a small country town. The plebiscite figures will probably be known before these notes are read, and it is hoped that the voting will show not only that the fight is on, but that it is on the way to be won.

"In Lighter Vein."

No meeting can be entirely grim when presided over by Dr. J. B. Miller, of Bishopbriggs, Lanarkshire. Behind a large pipe and a pair of gleaming spectacles he presents a deceptive air of somewhat bewildered benevolence which is much at variance with the excellent and expeditious way in which he carries out his duties. Chairman *de jure* by vote, he is chairman *de facto* by his personality—to the general satisfaction. While awaiting the arrival of one of the senior officials a question was raised as to the relevance of the remarks being made by the speaker at the rostrum: the chairman admitted that he, too, had doubts on the matter, but genially added, "he is filling in the time very usefully". When a later orator was challenged on a point of order it was ruled that "there does not seem to be much sense in what the speaker says, but he is quite in order in

saying it". Comments of this nature check waste of time better than any chairman's gavel. Towards the end of the meeting, however, the female of the species proved more deadly than the male. A lady representative closed a fervid denunciation of the act with the words, "The Australians have a National Health Service Act and it is inoperative because they won't work it", and then, turning towards the chairman, asked: "Why can't we all be Australians?" The thought of this national metamorphosis rocked the audience with laughter, and evidently shook even the iron composure of Dr. Miller, as for once no bolt fell from Olympus.

"Sign, Please."

A country doctor records in *The Times* that his real work of treating the sick is becoming of secondary importance in view of the number of medical certificates he is called on to sign. In one week his bag of such signatures included certificates for vacuum flasks, corsets, coal, brassières, hot-water bottles, elastic stockings, outsize shoes, milk, eggs, clothing coupons for expectant mothers, overseas travel, successful vaccination and inoculation, children's family allowance, glucose, "Horlick's Milk", brandy, whisky, petrol and paraffin. This is in addition to the usual certificates necessary in the case of panel patients for sick leave, absence from work and the like, some of which now have to be furnished in duplicate. In the correspondence that ensued mention was made of an application to enable an arthritic patient to have a lift installed in her house, and of another to buy a meat-mincing machine. The traditional illegibility of doctors' writing will no longer be traced "to taking notes when a student" but ascribed to penning plaintive and persuasive petitions to permit preferential purchase or procurement of proscribed products or of something in short supply.

Post-Graduate Work.

COURSES DURING MARCH, 1948.

THE Post-Graduate Committee in Medicine in the University of Sydney announces the following courses to be held in March, 1948.

WEEK-END COURSE AT ARMIDALE.

A week-end course will be held at New England University College, Armidale, in conjunction with the Northern District Medical Association, on Saturday and Sunday, March 6 and 7, 1948. The programme will be as follows:

Saturday.

2.5 p.m.: "Thrombosis", Sir Stanton Hicks; 3 p.m.: "The Surgery of Peptic Ulcer", Dr. B. T. Edye; 4.30 p.m.: "Cardiac Disease in General Practice", Dr. T. M. Greenaway; 8.30 p.m.: Symposium—"Nutrition: Its Place in the Prevention and Treatment of Disease": (i) "First Principles of Nutrition", Colonel H. F. White; (ii) "The Scientific Background of these First Principles", Sir Stanton Hicks; (iii) "The Surgeon's Application of the Principles of Nutrition", Dr. B. T. Edye; (iv) "The Physician's Practice of the Principles of Nutrition", Dr. T. M. Greenaway.

Sunday.

9.30 a.m.: "The Surgery of Common Duct Obstruction", Dr. B. T. Edye; 11.30 a.m.: "Neurological Problems in General Practice", Dr. T. M. Greenaway; 2 p.m.: "The Physiology and Pharmacology of the Heart and Blood Vessels", Sir Stanton Hicks.

Enrolments.

The fee for the course will be £1 1s. Those wishing to attend are requested to notify Dr. R. J. Jackson, Honorary Secretary, Northern District Medical Association, Armidale, New South Wales, as soon as possible.

COURSE AND EXAMINATION IN PRACTICAL BIOCHEMISTRY.

A practice period in preparation for the biochemistry examination will be held in the Biochemistry Laboratory, Old Medical School, University of Sydney, from 10 a.m. to 4 p.m. on Monday, Tuesday and Wednesday, March 8, 9 and 10, 1948. In addition to graduates enrolled for the September, 1947, degree and diploma courses Part I, who are expected to attend this practical course, enrolments will be limited to ten, preference being given to examination candidates. Early enrolment therefore is necessary and should be made without delay to the Course Secretary, the Post-Graduate Committee in Medicine, 131, Macquarie Street, Sydney. A fee of £1 1s. will be charged. The practical examination in biochemistry will take place on Friday, March 12, 1948, from 10 a.m. to 1 p.m.

FILM EVENINGS.

THE Post-Graduate Committee in Medicine in the University of Sydney announces changes in the presentation of its monthly film screenings to become effective from February, 1948. The programmes have been designed to include documentary and other films as well as those of purely medical interest, and the time of showing has been changed to an evening session beginning at 8 p.m. All medical practitioners are invited to attend, and inquiries should be made by communicating with the Secretary of the Post-Graduate Committee in Medicine, 131, Macquarie Street, Sydney, telephones B 4606 and BW 7483.

Correspondence.

SELF-INFLICTED PREFRONTAL LEUCOTOMY.

SIR: I have read the interesting report by Dr. H. V. Foxton in THE MEDICAL JOURNAL OF AUSTRALIA for November 22, 1947, page 645, of a soldier whose frontal lobes had been traversed ("leucotomized") by a rifle bullet at Suvla Bay in 1915, and who subsequently became "a very noticeably more cheerful person". Your readers may be interested to know of a case in my practice, similar inasmuch as the leucotomy was produced by a bullet, but in this instance self-inflicted in an attempt at suicide by a melancholic, who as a result of the frontal lobe injury lost his depression and developed a keenness to live. In June, 1937, a domestic man of all work, aged forty-eight years, shot himself in the head with a service revolver. The bullet passed through both frontal lobes from right to left. He did not succumb and his depression, the combined result of financial worry, exacting and uncongenial work, a domineering and difficult mother-in-law and a goading and garrulous wife, gave place to a mildly sustained euphoria, which is apparently far from leading him to a second attempt at suicide, and he now puts up with his difficulties cheerfully. Furthermore, he has had another to contend with, as he developed an osteomyelitis of the skull which necessitated several operations in addition to the primary one and kept him under my care for some time, but despite it all he has remained cheerful and was so when I saw him only last week.

Such self-inflicted dissipation of one's troubles along with the frontal lobes must be rare, but it adds to such evidence as is in favour of leucotomy for properly selected cases, and it would appear that for some at least we can now reply in the affirmative to Macbeth's question:

> Canst thou not minister to a mind diseas'd;
> Pluck from the memory a rooted sorrow;
> Raze out the written troubles of the brain?

Yours, etc.,

LAMBERT ROGERS.
Surgical Unit,
The Royal Infirmary,
Cardiff.
February 10, 1948.

Nominations and Elections.

THE undermentioned have applied for election as members of the South Australian Branch of the British Medical Association:

Kneebone, John Keith, M.B., B.S., 1947 (Univ. Adelaide), 62, Anzac Highway, Everard Park, South Australia.

Close, Rosemary Jocelyn, M.B., B.S., 1947 (Univ. Adelaide), 424, Gilles Street, Adelaide.

Madison, Thomas Glover, M.B., B.S., 1946 (Univ. Adelaide), Laught Avenue, Forrestville, South Australia.

Camens, Ivan Maurice Henry, M.B., B.S., 1947 (Univ. Adelaide), Cross Roads, Glen Osmond, South Australia.

The undermentioned has been elected a member of the South Australian Branch of the British Medical Association:

Barter, Robert Alexander, M.S., B.S., 1947 (Univ. Adelaide), Royal Adelaide Hospital.

Obituary.

GRACE FAIRLEY BOELKE.

WE regret to announce the death of Dr. Grace Fairley Boelke, which occurred on February 17, 1948, at Manly, New South Wales.

SYDNEY EVAN JONES.

WE regret to announce the death of Dr. Sydney Evan Jones, which occurred on February 17, 1948, at Leichhardt, New South Wales.

The Royal Australasian College of Physicians.

A LECTURE entitled "The Simulation of Heart Disease" will be delivered by Dr. William Evans, of the Cardiac Department, London Hospital, in the Stawell Hall of the Royal Australasian College of Physicians, 145, Macquarie Street, Sydney, at 8.30 p.m. on Friday, March 12, 1948. This lecture has been arranged by the President and Council of the College, but a cordial invitation is extended to all members of the medical profession to be present.

The Royal Australasian College of Surgeons.

NEW SOUTH WALES STATE MEETING.

A MEETING, open to all members of the medical profession, will be held in the Stawell Hall, the Royal Australasian College of Physicians, 145, Macquarie Street, Sydney, on Wednesday, March 3, 1948, at 4.30 p.m. A symposium on thoraco-abdominal surgery will be presented by Dr. M. P. Susman, Dr. F. W. Niesche and Dr. V. Kinsella. This meeting should be of special interest to surgeons studying for higher degrees.

Medical Appointments.

Dr. L. A. A. Forbes has been appointed government medical officer at Coolangatta, Queensland.

Books Received.

"British Surgical Practice", under the General Editorship of Sir Ernest Rock Carling, F.R.C.S., F.R.C.P., and J. Paterson Ross, M.S., F.R.C.S.; Volume I; 1947. London and Australia: Butterworth and Company (Publishers), Limited. 9½" × 6½", pp. 568, with many illustrations. Price: £3 17s. 6d.

"Treatment of Some Chronic and 'Incurable' Diseases", by A. T. Todd, O.B.E., M.B. (Edinburgh), M.R.C.P. (London); Second Edition; 1947. Bristol: John Wright and Sons, Limited. London: Simpkin Marshall, Limited. 8½" × 5½", pp. 338. Price: 25s.

"The Medical Clinics of North America" (issued every two months); 1947. Philadelphia and London: W. B. Saunders Company. Melbourne: W. Ramsay (Surgical) Proprietary, Limited. Philadelphia Number; 9" × 6", pp. 288, with illustrations.

"Chronic Structural Low Backache due to Low-Back Structural Derangement", by R. A. Roberts, B.Sc., M.B., Ch.B., D.M.R.E.; 1947. London: H. K. Lewis and Company, Limited. 9¾" × 7½", pp. 114, with many illustrations. Price: 45s.

"The Surgical Clinics of North America" (issued every two months); 1947. Philadelphia and London: W. B. Saunders Company. Melbourne: W. Ramsay (Surgical) Proprietary, Limited. Massachusetts General Hospital Number; 9" × 6", pp. 346, with many illustrations.

"Sir Frederick Banting", by Lloyd Stevenson, M.D.; 1947. London: William Heinemann (Medical Books), Limited. 9" × 6½", pp. 466, with illustrations. Price: 25s.

Diary for the Month.

MARCH 2.—New South Wales Branch, B.M.A.: Executive and Finance Committee, Organization and Science Committee.
MARCH 3.—Western Australian Branch, B.M.A.: Council Meeting.
MARCH 4.—New South Wales Branch, B.M.A.: Special Groups Committee.
MARCH 4.—South Australian Branch, B.M.A.: Council Meeting.
MARCH 5.—Queensland Branch, B.M.A.: Branch Meeting.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Honorary Secretary, 135, Macquarie Street, Sydney): Australian Natives' Association; Ashfield and District United Friendly Societies' Dispensary; Balmain United Friendly Societies' Dispensary; Leichhardt and Petersham United Friendly Societies' Dispensary; Manchester Unity Medical and Dispensing Institute, Oxford Street, Sydney; North Sydney Friendly Societies' Dispensary Limited; People's Prudential Assurance Company Limited; Phœnix Mutual Provident Society.

Victorian Branch (Honorary Secretary, Medical Society Hall, East Melbourne): Associated Medical Services Limited; all Institutes or Medical Dispensaries; Australian Prudential Association, Proprietary, Limited; Federated Mutual Medical Benefit Society; Mutual National Provident Club; National Provident Association; Hospital or other appointments outside Victoria.

Queensland Branch (Honorary Secretary, B.M.A. House, 225, Wickham Terrace, Brisbane, B.17): Brisbane Associated Friendly Societies' Medical Institute; Bundaberg Medical Institute; Brisbane City Council (Medical Officer of Health). Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

South Australian Branch (Honorary Secretary, 178, North Terrace, Adelaide): All Lodge appointments in South Australia; all Contract Practice appointments in South Australia.

Western Australian Branch (Honorary Secretary, 205, Saint George's Terrace, Perth): Wiluna Hospital; all Contract Practice appointments in Western Australia. All government appointments with the exception of those of the Department of Public Health.

Editorial Notices.

MANUSCRIPTS forwarded to the office of this journal cannot under any circumstances be returned. Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary be stated.

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